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Compliments of
The Division of Surgery
of
The Medical School of Harvard University.

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JUNE, 1903.

INTRODUCTORY.

J. COLLINS WARREN.

The following papers are presented by the surgical department of the Harvard Medical School as evidence of its ambition to encourage original work and to train men for research in the many branches of Surgery and Surgical Pathology. Apart from the study of cancer, for which there is a special fund, it is intended to continue the kind of work here represented, both in the laboratory and in the hospital.

We have been able to make a modest beginning with funds at present in our possession, derived partly from small endowments and partly from annual gifts.

The enthusiasm and capacity exhibited by the young men of this department for investigation of this character is most encouraging, and it is confidently expected that, with the almost ideal facilities which are to be given in the new buildings of the medical school, there will not be wanting talent worthy of the occasion. The new quarters for surgical research have been planned with the greatest care, and are on a scale which leaves nothing to be desired — except a suitable endowment. We cannot refrain from expressing great confidence in the belief that when the importance of the work in which we are engaged has been made clear to the public, generous patrons will be found willing to place this department of our labors upon an enduring basis.

HODGKIN'S DISEASE. — A PATHOLOGICAL ANALYSIS OF NINE CASES.

CHANNING C. SIMMONS.

(*From the Surgical-Pathological Laboratory, Massachusetts General Hospital.*)

(*For the Division of Surgery of the Medical School of Harvard University.*)

The following paper is a report of nine cases of Hodgkin's disease, in which pathological examination of the tumors was made. Eight of the cases were treated at the Massachusetts General Hospital and are included in this report through the courtesy of the visiting staff. Case IX. was a private patient of Dr. C. L. Scudder and is included with his permission. The author also wishes to express his thanks to Dr. William F. Whitney and Dr. J. H. Wright for many valuable suggestions.

Considerable misunderstanding seems to exist about the disease, and many do not seem to realize that it is a definite pathological process. Much of this confusion is undoubtedly due to the numerous synonyms, some, but by no means all, of which are the following: Pseudoleukemia (Cohnheim), malignant lymphoma (Billroth), Hodgkin's disease (Wilks), lympho-sarcoma (Virchow), adenie (Trousseau), desmoid carcinoma (Schulz). Of these names, lympho-sarcoma has probably occasioned the most confusion, as it suggests a sarcoma composed of lymphocytes, while in reality Hodgkin's disease is not a malignant growth, in the sense that it infiltrates, and is not composed exclusively of lymphocytes. It seems best, until a name has been evolved describing the pathological process, to call it Hodgkin's disease.

It was first described by Hodgkin in 1832,[1] who reported seven cases, several of which, however, were probably leukemia, syphilis, or tuberculosis. His paper was forgotten until Wilks[2] brought the subject up again in 1856 and 1865. Since then much work has been done, and the histological appearances of the glands described by many men, chief among whom may be mentioned Sternberg,[3] Fischer,[4] and

Goldmann.[5] The last important publication is by Reed,[6] who gives an exhaustive review of the subject and reports eight cases with their pathological findings.

Although the pathology is recognized, the etiology is very obscure, it having been classed as an infectious disease, as a form of true leukemia, and as sarcoma.

Leukemia. — Pinkus[7] mentions lymphocytosis in the blood as a common feature of the affection, and other observers have collected series of cases showing on examination of the blood all grades between the normal and true leukemia. The histology of the glands, however, in the two affections seems to be entirely different, and the blood when examined in this series of cases showed no signs of leukemia.

Sarcoma. — In some respects it does resemble a sarcoma, but it differs from a malignant growth in that only one kind of tissue is attacked — the lymph-adenoid — and it does not infiltrate, but it tends to extend from one group of glands to those in contiguity. The metastases in the liver, lungs, and other places can be explained as the disease attacking the small amount of lymphoid tissue normally present in those organs.

Infectious diseases. — Clark[8] in summing up his paper says that it resembles an infectious disease in that there are general symptoms with fever, it may run an acute or chronic course, it may remain local for some time and then become general, and the glands first involved are usually those nearest the skin. As regards culture experiments, Verdelli[9] has collected twenty-four cases where bacteria were present in the blood at some stage of the disease, and other cases have been reported, but there is no uniformity in the observations. Delbet[10] claims to have caused the disease by inoculating a dog with a bacillus obtained from the blood of a patient suffering from Hodgkin's disease, but his proof is not convincing, and the experiment has never been repeated.

The etiological theory that seems to have the greatest number of supporters is that the disease represents an atypical form of tuberculosis. Sternberg is the main exponent of this view, and has reported a series of thirteen autopsies on cases where the clinical diagnosis of Hodgkin's disease was made, in which series he found tuberculosis present in eight. Crowder[11] has demonstrated tubercle bacilli in glands which histologically had the appearance of Hodgkin's disease. Other men, while admitting the common occurrence of tuberculosis in the disease, consider it as a secondary infection which might well be expected to occur in debilitated patients (Fischer, Goldmann, and Reed). Reed, although demonstrating in one of her cases tubercle bacilli in a typical Hodgkin's gland, believes that the two processes were distinct, but co-existent.

The conclusions reached from the examination of this series of cases agree with those of the last-mentioned observers. It was impossible to demonstrate tubercle bacilli in any of the glands examined, nor could any be found in the glands or organs of the animals inoculated with pieces of the tissue. Tuberculosis, unrecognized clinically, was present in two of the three cases which came to autopsy, but the histological picture of the two processes had nothing in common. No gland examined was affected with both tuberculosis and Hodgkin's disease.

There is general uniformity in the description of the gross pathological findings of the various observers. There is an increase in size of the lymph nodes, those of the neck being usually first affected, which, although they may become enormously enlarged, do not infiltrate, but remain discrete. The lymph glands in all parts of the body may become affected, the disease, as a rule, extending from one group of glands to those in contiguity. On section, these glands are usually described as soft, of a grayish-white color, and homogeneous, and have an almost characteristic bulging appearance. Some are hard and on section dense and fibrous. As the process advances, metastases may be found in any of the organs, where they have the same general appearance as the

glands, but are of irregular shape and infiltrate the tissue. They may be found almost anywhere in the body. The spleen may or may not be affected and enlarged. Tuberculosis is often present in some organ of the body.

MICROSCOPIC EXAMINATION OF SPECIMENS FROM THE NINE CASES.— The specimens were all hardened in Zenker's fluid and embedded in paraffin. They were stained with hematoxylin and eosin as a routine, and all were also stained with carbol fuchsin, in an endeavor to demonstrate tubercle bacilli, twenty-five per cent nitric acid and ninety-five per cent alcohol being used as a decolorizer. In most cases specimens were also stained with Mallory's connective tissue stain, while in many some slides were stained with iron hematoxylin and orange G.

The examination showed in the main the same histological features as have been described by many other observers. The process consists essentially of a proliferation of the reticulum, with a resulting marked increase of fibrous tissue. Reed describes the earliest change as a proliferation of the endothelial cells covering the reticulum and of the cells in the center of the follicles. These cells infiltrate the lymph spaces and soon make the follicles indistinguishable, entirely destroying the normal appearance of the glands. In none of the specimens examined was the process in as early a stage as this, and in none could the follicles be distinguished, the lymph spaces being filled with large epithelioid cells and lymphocytes. As the process advanced, there seemed to be a very marked increase of the reticulum, with a corresponding decrease in the cellular elements, until a dense tumor was formed, consisting mainly of fibrous tissue in which a few small cellular islands could be distinguished. Macroscopically these glands were composed of bands of dense fibrous tissue separating small islands of more or less translucent gray color. The

size of the gland had no relation to the stage of the disease, and, clinically, fluctuated markedly.

The lymph spaces were usually filled with cells. The vessels in the more cellular specimens were dilated, and the connective tissue seemed rather more abundant around them than elsewhere. In the fibrous specimens the vessels were decreased in number. Necrotic areas of varying size were present in nearly all the specimens, and in these the nuclei showed fragmentation, and polymorphonuclear leucocytes were present. The large epithelioid cells were usually more abundant around these areas than elsewhere.

Cellular elements. — The specimens were composed mainly of the larger and smaller forms of lymphoid cells and large epithelioid cells more or less differentiated. The derivation of these cells was not clear, but many seemed to be intimately associated with the reticulum. These epithelioid, or endothelial, cells varied greatly in appearance, but were all apparently derived primarily from the same cell, as all grades of variation could be seen between the two extremes. They were found in varying positions, some loose in the tissue, while others seemed to have marked protoplasmic processes and were connected closely with the reticulum. In one form the cell was oval, with considerable clear staining protoplasm and one vesicular nucleus containing one or more large nucleoli. This form may be considered nearest to normal, as somewhat similar cells were seen in a hyperplastic lymph gland. In some specimens many of these cells showed mitotic figures. Others were irregular in shape, and contained one or more round, oval, or irregular nuclei, sometimes centrally, at others peripherally, placed. In these cells the cytoplasm was of relatively small amount. In some it was granular, while in others it appeared to have protoplasmic processes. Vacuoles were often seen in these cells.

Giant cells were present in varying numbers in all the specimens, and varied greatly in size, some of them being as large as forty-five micro-millimeters in diameter. They were of irregular shape, and contained from two to five, or more, vesicular nuclei, having no particular arrangement. In some

the nuclei were much smaller than in others, and the cytoplasm darker. Vacuoles were often seen in these cells. The giant cells did not resemble in any way the typical ones of tuberculosis. Giant cells somewhat resembling these were seen, however, in an affected gland from the neck of a case of lympho-sarcoma, the term being used in the restricted sense primary in the tonsil. The tumor occurred in one tonsil, which was removed, and six months later in the other.

The gland examined was from the neck, and was removed three years later, at which time the glands and muscles were infected. These differed in that they were phagocytic, nearly all containing red blood corpuscles, while none were ever seen in the giant cells in this series of nine cases. No giant cells were seen in two cases of lymphatic leukemia, one case of mycosis fungoides, or in two cases of multiple small round-cell sarcoma of the skin.

Lymphoid cells were present in all the specimens, and in most were the commonest cellular element. Both the larger and smaller types were present.

Eosinophiles were present in varying numbers in seven out of the nine cases examined. Goldmann first called attention to these cells, and in an examination of lymph glands from thirty cases of various other diseases only found them in two — in a case of erysipelas and in one of salpingitis. In the specimens examined they varied greatly in number. In Case IX. they constituted nearly half the cells seen in some fields. They also varied in different glands from the same case.

Degenerating cells, represented by cells with dense nuclei and deeply staining protoplasm, were seen in all specimens in varying numbers. Plasma and mast cells could be found on search, but were never present in striking numbers.

ANALYSIS. (See table.) Of the nine cases examined, three came to autopsy (Cases I., III., IV.). Case VIII. died, but no autopsy was allowed. Of the remaining five, three have been lost track of (Cases II., V., and VI.), one is slowly progressing (Case VII.), and one is as reported, too short a time having elapsed since the examination for further symptoms to develop.

Of the cases, seven were in adults, two in males, and five in females, and two in children, one boy and one girl. This is rather unusual, as statistics show the disease more prevalent in young males. In six cases the symptom for which the patient sought medical advice was swelling of the glands in the neck. In two cases (Cases III. and IV.) the glands chiefly involved were post-peritoneal, but they were also present in the neck. In one (Case IX.), the mediastinal.

Tuberculin was given three times, twice with a negative result (Cases III. and. IV.), and once with the positive (Case VIII.). In one of the cases (Case III.) with a negative reaction tuberculosis was found present at the autopsy. Tuberculosis was present in some part of the body in two of the three cases that came to autopsy. These two cases, together with Case VIII., which clinically showed tuberculosis of the lung, and also gave a positive test with tuberculin, make tuberculosis positively present in three of the nine cases.

A differential blood count was unfortunately only made in six of the cases, and in most of these only once (Cases III., IV., VI., VII., VIII., and IX.). In none did it show any evidence of leukemia. Where a leucocytosis was present it was due to the polymorphonuclear neutrophiles, and usually could be accounted for.

No conclusions as to the changes in the bone marrow can well be drawn, as it was only carefully examined in one case.

Subcutaneous inoculation of animals with pieces of the glands was done in five cases (Cases IV., VI., VII., VIII., and IX.), with negative results as regards tuberculosis.

Eosinophiles were present in the glands in varying numbers in seven cases, being absent in Cases I. and IV.

From the analysis and from the microscopic examination of these cases, there seems to be no reason for classing the disease as a form of leukemia, as the blood examinations were all negative as regards that disease, and the histological changes in the glands in the two affections have practically nothing in common. Furthermore, if the lymphocytes originate in the glands, there is no reason to expect an increased

number of these cells in the blood, as the change is essentially a fibrous one, and not an increase in the cellular elements or "hyperplasia," as it is often erroneously termed.

As regards tuberculosis, as has been said before, all attempts to demonstrate the bacilli, either by histological methods or by the inoculation of animals, failed.

The presence of eosinophilic leucocytes in the glands is suggestive, and in doubtful cases, particularly in the later or fibrous stage of the disease, may be of assistance in diagnosis, but is by no means to be relied upon.

CONCLUSIONS.

1. Hodgkin's disease should be regarded as an entity, and presents a definite histological picture.

2. It has no relation to leukemia or tuberculosis, although the latter may be co-existent.

3. Eosinophiles are often though not always present in the glands.

	M.	F.	Child.	Tbc.	Inoculation.	Autopsy.	Eosinophil.	Blood as at Leuk.	Glands first noticed in
Case I.		+				complicating tbc.	none		neck.
Case II.		+		negative			some		neck.
Case III.	+			negative		complicating tbc.	marked	negative	mainly post-peritoneal, present in neck.
Case IV.		+			negative	no tbc.	none	negative	mainly post-peritoneal, present in neck.
Case V.		+	+				some		neck.
Case VI.		+			negative		some	negative	neck.
Case VII.	+				negative		marked	negative	neck.
Case VIII		+		positive	negative		marked	negative	neck.
Case IX.	+		+		negative		extreme	negative	over sternum.

The following are the histories and pathological findings of the cases in abstract. To avoid useless repetition, the histology of the specimens is not given in full, but only the more important points noted. In all, cells of the different types described were seen in varying proportions.

CASE I. — Dr. F. C. Shattuck. Female, 24, single. Dec. 21, 1901.

Family history not important. Previous history, always in good health, except an occasional sore throat.

Present illness. — Two months ago "caught cold," which left her with a hacking cough without sputum. Two weeks later left side of neck became somewhat swollen; shortly after, right side, which soon exceeded the left in size. Swellings slightly tender, and at times painful. Two weeks before date complained of some difficulty in swallowing and dyspnœa. Has lost considerable strength during last month.

Physical Examination. — Well-developed and fat. Eyelids puffy. Throat injected. On each side of the neck and in the posterior triangle is a smooth, soft swelling, reaching from the clavicle to behind the ears. Circumference of the neck 16.5 inches. No discreet glands felt. No glands in the axillæ or groins. *Chest:* Superficial veins dilated. A few fine rales heard at apices front and back. On percussion, heart and liver dullness normal. From the base of the heart marked dullness extends to the sternal notch and for .75 of an inch to the right and two inches to the left of the sternum. *Heart:* Sounds normal. *Abdomen:* Normal. *Spleen:* Not enlarged to percussion or palpation.

Urine not remarkable.

BLOOD. — Hemoglobin, 90 per cent. Whites, 8,000. No red or differential count made.

Temperature during stay in hospital was irregular, varying between 100° and 103° C. Pulse and respiration not remarkable.

After admittance to the hospital patient grew worse with increasing dyspnœa and cyanosis, and died Jan. 1, 1902.

AUTOPSY. — Anatomical diagnosis. Round-cell sarcoma of mediastinum with metastases in pericardium, liver, kidney, and lung; tubercular ulcerations in intestines; tuberculosis of the Fallopian tubes, mesenteric, lymph glands, and kidney; polyp of intestine with tubercular base undergoing adeno-carcinomatous change.

Well-developed and nourished. Conjunctival edema. Muscles pale. No fluid in peritoneal cavity. *Liver:* Four fingers' breadth below costal margin and surface presented gray-white adhesions to the diaphragm. *Spleen:* Also presented adhesions. On the liver in several places were several dense, white areas which showed through the capsule. These on section were firm, white nodules a few millimeters in diameter. Similar nodules were present in the substance of the organ. No nodules in spleen or adrenal. *Kidneys:* Combined weight two hundred and seventy-four grams. In one, surface presented three gray, slightly bulging areas, the largest two centimeters in diameter. On section these extended into the tissue as masses of gray-white new growth, with sharply marked borders.

A similar mass in the substance of the organ. At one pole of the other kidney were three cysts, the largest two centimeters in diameter. One contained clear fluid, while the other two had fibrous walls with yellowish areas in them, and contained thick, yellowish-white pus. *Tubes:* Slightly thickened, and walls showed minute yellowish areas. Peritoneum over these whitish and thickened. Other pelvic viscera normal. *Intestines:* From forty-two centimeters above to the ileo-cecal valve were nine places where the walls were thickened and the lumen constricted. The peritoneum over these thickened and showed yellowish nodules. At these places were one or more irregular moth-eaten ulcerations in the mucosa, from the base of which yellowish pus could be expressed. *Mesentery:* Thickened and showed glands with yellowish-white areas on section. *Lungs:* Bound to chest wall everywhere by adhesions. In the upper portion of the thorax was a new growth adherent to the pericardium, extending around the heart and cementing the pericardium and pleuræ together. It measured roughly eleven by fifteen centimeters. Extended upward slightly beyond sternum and pressed on great vessels, bronchi, and trachea. The growth on section was firm, lobulated, and of a grayish-white color, with a few yellowish areas. The pericardium was thickened, and showed numerous whitish nodules on its inner surface. On the visceral pleura were several whitish areas. No nodules seen in the lungs.

Microscopic examination of the lobules of growth from mediastinum showed it to consist mainly of lymphoid cells and large irregular cells with vesicular nuclei, and a small amount of protoplasm. There was a marked increase of the reticulum in comparison with that of a normal lymph gland, and in places dense bands of fibrous tissue divided the more cellular parts of the specimen. In the larger cells the nuclei were of irregular size and shape. The lymphoid cells were of the common type. Besides these, there were many large cells, with two or more vesicular nuclei and a greater amount of protoplasm. Some of these showed mitotic figures. Occasional giant cells with many large nuclei were seen. No eosinophiles seen in any section. Scattered throughout the section were a few necrotic areas infiltrated with leucocytes. *Lung:* Scattered through a good-sized section large areas of lung tissue were seen infiltrated with cells similar to those in the mediastinal tumor. Otherwise the lung showed edema and considerable desquamation of the epithelium. *Kidneys:* Section through the tumor showed the character of the growth to be the same as that in the mediastinum, with the exception that there was comparatively little fibrous tissue. The cells were of epitheliod type for the most part, and giant cells were fairly numerous. The nodule was not sharply separated from the renal tissue and faded gradually into it. Otherwise the kidney was not remarkable. A section through the wall of one of the cysts of the other kidney showed it lined with granulation tissue in which many epithelioid cells were present. Several Langhans giant cells were seen. The histological picture was that of undoubted tuberculosis. The interstitial tissue of the kidney in the neighborhood was increased. Sections of the

intestine and Fallopian tubes also showed undoubted tuberculosis. Section of the polyp showed beginning adeno-carcinoma and tuberculosis.

No inoculation experiments were made.

CASE II. — Dr. E. G. Cutler. Female, 26, single. March 31, 1902.

Family and previous history not remarkable. Present illness: one year ago had a cold followed by dry, hacking cough which has persisted until the present time. Shortly after noticed some lumps in the right side of the neck, which were removed in a local hospital nine months ago, but they recurred shortly after the operation. At this time a severe pruritis developed, which has persisted until the present time, causing insomnia. Lately much dyspnea and pain in the neck. Has been hoarse for the last month. Has lost some strength and weight.

Physical Examination. — Well-developed and nourished. Body covered with excoriations. Color and eyes normal. In posterior triangle of neck on both sides are many discrete glands varying up to, roughly, five centimeters in diameter. These are not tender or painful and are freely movable. Paralysis of both vocal cords, more especially right, due probably to pressure on recurrent laryngeal nerve. Right arm slightly swollen and cyanotic. Small gland felt in right axilla. None in other axilla or groins. *Chest:* On percussion dullness in front extends from base of the heart to the clavicles and one inch to the right and one to the left of the sternum. Heart apex, fifth space nipple line. Soft, systolic murmur heard at apex, transmitted into axilla; pulmonic second accentuated. Over dull area in front breathing high-pitched and expiration prolonged. Elsewhere normal.

BLOOD. — Hemoglobin, 85 per cent. Whites, 11,000. No red or differential count made.

Urine normal.

Temperature, somewhat irregular, between normal and 100° C. Pulse and respiration not remarkable.

Tuberculin given April 3, with negative result.

A gland was removed from right side of neck April 3 for diagnosis. Patient was discharged June 20, 1902, in practically the same condition as at entrance.

Pathological Examination. — The specimen consisted of an oval tumor three centimeters in its longest diameter, covered with a capsule of fibrous tissue. On section it was bulging, soft, of a grayish-white color and semi-translucent. A few ill-defined connective tissue trabeculæ could be seen running through it.

Microscopic examination showed no structure of the normal lymph gland. In no place could the follicles be distinguished. It was divided into lobules by dense bands of fibrous tissue. Between these the growth consisted mainly of lymphoid cells, but there were many larger cells with vesicular nuclei and a small amount of protoplasm. In one part of the specimen, in addition to these, were larger numbers of still larger cells with

considerable protoplasm, and one or more nuclei. These often showed mitoses, and seemed to occupy often the position of the lymph sinuses, but occurred anywhere in the tissue. Others appeared intimately connected with the reticulum. Giant cells were common. The reticulum was increased, but not to the extent seen in some of the other cases. A small necrotic area was present, in one place infiltrated with lymphocytes. Around this the epithelioid and giant cells exceeded in number the lymphocytes. A few eosinophiles were seen. (Plate XV., Fig. 1.)

Case III. — Dr. E. G. Cutler. Male, 48, married. Dec. 20, 1901.

"Quinsy sore throat" for five successive years. Two years ago caught cold, and for one month had chills and fever occurring fairly regularly every second day. This was followed by anorexia, loss of weight and strength, which has persisted until the present day. Never had any definite symptoms. Has been growing weaker and not able to work for six months. For last three weeks has been considerably worse and has noticed some edema of the ankles and dyspnea on exertion. Slight cough recently.

Physical Examination. — Fairly-well nourished. Skin pale and dry, and some brownish pigmentation on the back. A few small discrete glands felt in the posterior triangles of the neck on both sides, and also in the axillæ and groins. *Heart* and *lungs* normal. *Abdomen:* Spleen not enlarged. *Liver:* Normal. An indefinite tumor mass felt in the epigastrium. Stomach capacity seventy-two ounces. Examination of the sputum failed to show tubercle bacilli.

Tuberculin given January 19 with negative result. The spleen was slightly enlarged on February 19, and an indefinite mass palpable over the right kidney. The patient died April 2, 1902. During the stay in the hospital he failed slowly, having no definite symptoms, or changes in physical signs.

The temperature was very irregular, between normal and 103. Pulse and respiration not remarkable.

Urine not remarkable.

Blood. — December 24. Hemoglobin, 75 per cent. Whites, 13,600.

Polymorphonuclear neutrophiles		62	per cent.
Basophiles	large	23	"
	small	13	"
Oxyphiles		2	"

No blasts seen. Much achromia.

February 9. Hemoglobin, 45 per cent. Reds, 4,096,000. Whites, 6,000.

Polymorphonuclear neutrophiles		76.0	per cent.
Basophiles	large	8.5	"
	small	15.0	"
Oxyphiles		.5	"

February 28. Hemoglobin, 35 per cent. Reds, 2,496,000. Whites, 9,300.

Polymorphonuclear neutrophiles		87.5 per cent.
Basophiles	large	1.0 "
	small	20.0 "
Oxyphiles		.5 "

No blasts seen. Some achromia.

March 18. Hemoglobin, 20 per cent. Reds, 1,944,000. Whites, 3,600.

Polymorphonuclear neutrophiles		67.3 per cent.
Basophiles	large	8.5 "
	small	23 7 "
Oxyphiles		.5 "

AUTOPSY. — Anatomical diagnosis. Pseudo-leukemia of retroperitoneal lymph glands, spleen and liver; general anemia; chronic hyperplasia of the spleen; fibroid atrophy of the narrow of the vertebra; hyperplasia of the marrow shaft of the femur; focal tuberculosis of the lung.

Skin pale. Edema of the ankles. Considerable fluid in the peritoneal cavity. One thousand centimeters of clear fluid in each pleural cavity. Left lung bound to parietal pleura by firm adhesions. Few adhesions at right apex. *Right Lung:* Near the apex a resistant area two by four centimeters, on section consisting of dense, fibrous bands separating semi-calcified areas. Similar area near apex of left lung, which on section consisted of grayish translucent nodules separated by fibrous tissue. In the center of this was a cheesy mass four millimeters in diameter. In the inferior lobe were similar areas four centimeters in diameter. *Heart:* Excess of serous fluid in pericardial sac. *Liver:* Not remarkable. *Spleen:* Weight three hundred and eighty-one grams. On section it was generally of a reddish-brown color, but scattered through it were several grayish-white, translucent areas. *Kidneys*, *Pelvic*, *Viscera*, and *Intestines* not remarkable. *Stomach:* Contained several small, soft polypi. In the retroperitoneal region on each side and in front of the aorta was an irregular tumor mass roughly sixteen by seven centimeters in diameter. On section this consisted of masses of irregular, ovoid tumors of a grayish, translucent, firm tissue. Attached to the pancreas was an ovoid tumor two centimeters in diameter, resembling a lymph gland on section. In the bodies of the lumbar vertebræ the fat was in excess of the red bone marrow. The shaft of the femur contained dark red marrow.

Microscopic Examination. — Sections from different parts of the tumor showed various stages, from a simple hyperplasia of the follicle to a dense gland formed mainly of fibrous tissue. A section of the retroperitoneal gland showed marked increase in the reticulum. No follicles could be distinguished. The blood vessels were fairly numerous and many showed endo-arteritis. The cells were mainly lymphoid. Epithelioid cells of varying size and shape with vesicular nuclei were common. A rare giant

cell was seen. A marked feature of the specimen was the number of eosinophiles present. A section from a gland near the pancreas showed somewhat the same picture, only the fibrous tissue was considerably less. *Spleen:* Sections of the nodules showed them to be the same as the retroperitoneal tumor. Some of the follicles of the spleen were hyperplastic, while others were more or less transformed into fibrous tissue. Eosinophilic leucocytes were present in all parts of the spleen. *Liver:* The connective tissue about the bile ducts was increased and contained many small, round cells, eosinophiles, and a few cells of the epithelioid type. *Lung:* Showed well marked typical tubercular lesions of essentially the chronic type. *Marrow:* (*a*) Of femur showed extensive replacement of the fat tissue by marrow cells in most places, but in one part of the section it was not replaced, but necrotic. Among the marrow cells were many eosinophilic leucocytes. No megaloblasts were definitely recognized. (*b*) Of vertebra — the marrow spaces were largely filled with connective tissue, which in places contained marrow cells. The general impression was that the fat and marrow were extensively replaced by connective tissue.

No inoculation experiment was made.

Case IV. — Dr. S. J. Mixter. Female, 55, widow. June 18, 1902.

Family and previous history not remarkable. Present illness, has been weak and lost considerable weight and strength in the last few months, but has never had any definite symptoms until about seven weeks ago, when she had an attack of indigestion characterized by pain in the epigastrium, occurring usually after meals, accompanied by nausea and vomiting. The vomitus consisted of large quantities of sour-tasting material and never contained any blood. Jaundiced since beginning of the attack. Six weeks ago had an attack of sharp pain in the right side of the chest and back, relieved by local treatment. Appetite poor. Constipated.

Physical Examination. — Well-developed and nourished. Skin and conjunctivæ yellow. A discrete, freely movable gland in the right posterior cervical triangle just above the clavicle the size of a hen's egg. Several other small ones in left. None in axillæ. Few in groins. *Chest:* Hyper-resonant on percussion. A few moist rales heard in the back. At the right apex voice sounds and resonance increased and a few fine rales heard on coughing. *Heart:* Apex in sixth space 4.5 inches from the sternum. Sounds faint. Soft systolic murmur at the base not transmitted. *Abdomen:* Liver two centimeters below the costal border. Apex of spleen palpable. Slight tenderness in epigastrium.

Urine showed bile and hyperemia.

The temperature varied from 98.6 to 102° C. Pulse and respiration not remarkable.

An exploratory laparotomy was done on June 27. The patient died three days later.

Blood. — Hemoglobin, 55 per cent. White count, 66,000.

Polymorphonuclear neutrophiles		85 per cent.
Basophiles	large	11 "
	small	4 "
Oxyphiles		1 "

AUTOPSY. — Anatomical diagnosis. Pseudo-leukemia of retroperitoneal, omental, supraclavicular, and pericardial lymph nodes and of the spleen; broncho-pneumonia; amalaceous secretions in the lung; icterus; accessory spleen; polyp of uterus.

Skin and conjunctivæ yellow. Moderate swelling in left supraclavicular region; two hundred to three hundred cubic centimeters of fluid in the pelvis. Large amount of peritoneal and omental fat, in which were many ill-defined areas of grayish, fairly firm tissue, the largest a few millimeters in diameter. In the greater omentum, near the stomach, were several rounded lymph-node-like nodules, the largest three centimeters in diameter, which consisted of soft, gray, homogeneous tissue. These had a definite capsule and resembled lymph nodes. The anterior surface of the lesser omentum showed many flattened nodules of the same tissue, and on section through these a conglomerate mass of numerous oval nodules of rather whitish, soft homogeneous tissue was disclosed. These varied up to two centimeters in diameter. The mass was connected with a second, lying about the pancreas and aorta, which was composed of larger nodules, varying up to seven centimeters in diameter, and which was situated, in general, between the pancreas and liver, but was continued downward along each side of the aorta, and occupied the situation of the post-peritoneal lymph glands. All had a similar appearance to the nodules in the omentum. They had definite fine capsules and were loosely bound together. The mesentery near its root was invaded with similar nodules. *Spleen*: Weight, seven hundred and sixty-two grams. On section it was thickly sown with similar gray nodules varying up to four centimeters in diameter. Some were yellow, suggesting necrosis. *Liver:* Normal. Other abdominal and pelvic viscera not remarkable. *Thorax:* Left lung was bound to pleura by adhesions. In inferior lobes of both were two or three ovoid tumors similar to those elsewhere. No mediastinal or bronchial lymph glands. *Heart;* Normal. In the left supraclavicular region was a group of tumor nodules similar to the others.

Microscopic Examination. — Sections of the glands from various places showed about the same condition. All were very cellular and contained comparatively little fibrous tissue which, however, was more marked in some than in others. A section from a retroperitoneal gland showed it to be composed mostly of large epithelioid cells of varying shape and size, with large vesicular nuclei. The protoplasm often contained vacuoles. A few vessels could be seen, and the section showed necrotic areas, in many places infiltrated with polynuclear leucocytes. Many giant cells were present. Lymphoid cells were scattered through the section in small groups. (Plate XVI., Fig. 1.) *Spleen:* Showed a large amount of the

same tissue which was extensively necrotic. Where not invaded it showed a marked increase in fibrous tissue. *Liver* and *Kidneys* not remarkable. *Lung*; Showed, in places, the air cells filled with a pneumonic exudate and presented the typical picture of a bronchial pneumonia. The marrow of the shaft of the femur showed the fat tissue much infiltrated with marrow cells.

Two guinea-pigs were inoculated subcutaneously on June 27. One with a small piece of the spleen, and the other with a bit of the growth. They were killed October 2. The autopsies failed to show any signs of tuberculosis.

CASE V. — Dr. S. J. Mixter. Female, five years. June 26, 1902.

Child has always been weak, often suffering from colds and diarrhea. At present has otitis media. For one year the parents have noticed a growing swelling on the left side of the neck. General condition the same as one year ago.

Physical Examination. — Poorly nourished. Examination of the chest and abdomen failed to show anything abnormal. On the left side of the neck, anterior to the mid point of the sterno-mastoid, is a discrete, oval swelling the size of a hen's egg, — not tender and freely movable. There are many small, discrete glands in the posterior triangle on the left and anterior triangle on the right. No glands in axillæ or groins.

Temperature, pulse, respiration, and urine not remarkable.

Pathological Examination. — Specimens consisted of several roughly oval, discrete nodules, varying from three to six centimeters in their greatest diameter. They showed a distinct capsule, and were loosely bound together by fibrous tissue. On section they were soft, homogeneous, of a yellowish-gray color. A few ill-defined fibrous trabeculæ seen near the capsule.

Microscopic examination showed no markings of the normal lymph glands. The sinuses were filled with cells. There was considerable increase in the reticulum. The cells, for the most part, were small lymphoid cells, but others with vesicular nuclei and a varying amount of protoplasm were abundant, being more common in some parts of the specimen than in others. Some were regular in shape, while others showed protoplasmic processes, and were intimately connected with the reticulum Blood vessels were fairly numerous and showed some endo-arteritis. A few eosinophiles were seen on search.

No inoculation experiments were made.

CASE VI. — Dr. H. F. Vickery and Dr. F. B. Harrington. Female, 54, widow. July 21, 1902.

Rheumatism ten years ago. Otherwise always well. Present illness: Grippe two years and a half ago, which was followed by a persistent cough with considerable sputum. Nineteen months ago she noticed a swelling under the left ear, soon followed by a similar one on the right side of the

neck, which became the size of a goose egg in one month. At the same time smaller ones appeared above the clavicles, and she began to lose weight and strength. Three months later the swellings decreased in size and disappeared (?) in six months, while similar ones appeared in the axillæ and groins. For about a year she has had pruritis and night sweats, and has noticed a brownish pigmentation of the skin.

Physical Examination. — Well-developed, poorly nourished. Body perspiring and excoriated. Skin thickened and brown. Some edema of the ankles. In the triangles of the neck on both sides, and in the axillæ and groins are masses of hard, discrete glands varying up to four centimeters in diameter. *Heart:* Soft, systolic murmur, not transmitted, heard at apex and base. *Lungs:* normal. *Abdomen:* Spleen not enlarged. In the lower part a vague, irregular mass could be felt.

Urine, pulse, and respiration normal.

The temperature varied between normal and 100.

Blood. — Hemoglobin, 65 per cent. White count, 25,800.

Polymorphonuclear neutrophiles		81 per cent.
Basophiles,	large	13 "
	small	5 "
Oxyphiles		1 "

Some glands were removed from the groins August 8. Discharged unimproved August 31.

Pathological examination of a gland removed from the axilla, April 2, 1902, showed a firm, grayish nodule, two centimeters in diameter, invested with a tough capsule. On section it was composed of small areas of grayish, homogeneous tissue separated by dense fibrous septa.

Microscopic Examination. — The specimen consisted mainly of dense bands of connective tissue which separated small cellular areas. These were composed almost wholly of lymphoid cells. A few irregular, large cells with vesicular nuclei could be seen, which seemed to be connected with the reticulum. A few degenerated cells were seen, but no giant cells. There were very few vessels. (Plate XV., Fig. 2.)

The mass from the groin removed August 8 consisted of a number of rather soft, ovoid glands, varying from two to six centimeters in diameter. They were invested with a thin, fibrous capsule and loosely bound together. On section they were bulging and composed of fairly firm, homogeneous grayish tissue.

Microscopic examination of a gland showed what might be termed the cellular type of the disease. There was no evidence of any follicles. The reticulum was increased and present in fairly uniform amounts. Of the cellular elements the lymphoid cells predominated. There were, however, great numbers of the larger cells, with vesicular nuclei and protoplasm of various amounts. These cells were both free and connected with the reticulum, and many showed mitotic figures. Giant cells were abundant, and eosinophiles fairly common. The capsule was thickened and infiltrated with large cells and lymphocytes.

A pig was inoculated August 8 with a piece of a gland and killed October 2. The autopsy revealed nothing abnormal.

Case VII. — Dr. F. B. Harrington. Male, 39, married. Sept. 2, 1902. Family and previous history not remarkable. Three weeks ago he noticed a bunch on the right side of neck which has increased rapidly in size until the present time. For the last three days he has had some dyspnea and difficulty in swallowing.

Physical Examination. — Well-developed and nourished. Throat negative. In the posterior cervical triangle, on the right, is a large mass of discrete glands, the largest of which is twelve centimeters, roughly, in diameter. A few smaller ones are present in the corresponding triangle on the left. None in axillæ. A few small, hard glands in both groins. *Chest:* Heart normal. *Lungs;* expiration slightly prolonged at right apex, otherwise normal. *Abdomen:* Spleen and liver of normal size.

Urine, temperature, pulse, and respiration not remarkable during his six days' stay at the hospital. The glands during this time decreased notably in size.

On Jan. 19, 1903, the glands in the neck were about the same as at discharge. Several discrete glands were present in the right axilla, the largest, roughly, four centimeters in diameter. A few smaller ones could be felt in the left axilla and in the groins. *Chest:* Normal. *Spleen:* Not enlarged. On April 15 the glands in the neck had increased somewhat in size, but, the patient said, varied considerably. The superficial veins over the right pectoral muscle were considerably dilated. On percussion to the right of the upper half of the sternum anteriorally was an indefinite area of diminished resonance, over which the breathing was somewhat harsh. The general condition was excellent.

Pathological Examination. — The specimen consisted of a few discrete lymph nodes from the neck, varying up to two centimeters in their greatest diameter. On section they appeared to bulge and were invested with fine fibrous capsules. They were homogeneous, and of a translucent grayish-yellow color. In some of the glands a few fine fibrous trabeculæ were seen dividing them into lobules.

Microscopic Examination. — Presented a picture almost identical to that described in the two preceding cases. There was no structure of the normal lymph gland to be made out. Lymphoid cells with the commonest cellular elements, but large, irregular, endothelial cells, were present in great numbers. Giant cells were also frequently seen, and there was a considerable number of eosinophiles. Plasma cells were present in larger numbers than in any other specimen, but were not a striking feature. Blood vessels were numerous.

Inoculation. — A pig was inoculated September 2 subcutaneously with a bit of a gland, and killed October 25. The autopsy showed the glands in the mediastinal axillæ, groins, and post-peritoneal considerably enlarged.

Microscopic examination of these glands showed simple hyperplasia and no evidence of tuberculosis, nor could the bacilli be demonstrated in sections especially stained for them.

CASE VIII. — Dr. C. B. Porter, Dr. F. C. Shattuck, Dr. E. G. Cutler. Female, 26, single. Nov. 21, 1902.

In October, 1899, noticed a swelling in the left side of her neck. Was examined at this time in the Out-Patient Department, and dullness and a few fine rales were found at right apex. In January, 1900, was sent to the Rutland Sanitorium for tuberculosis. While there had night sweats, but no tubercle bacilli were ever demonstrated in sputum. In August, 1901, a mass of glands was removed from the right side of the neck and right axilla at another hospital, but they recurred at once. They were removed again in May, 1902, but no pathological examination was made. At this time tuberculin was given with marked reaction. Three months ago the glands recurred in the left neck and axilla, and others appeared in the right side of the neck and axilla. Considerable cough and sputum for three years. Pruritis for last three months.

Physical Examination. — Fairly well-developed and nourished. In the left posterior cervical triangle are many small, firm, discrete glands not tender and freely movable. There is a similar mass on the right side, extending from behind the ear to the clavicle, and a freely movable rounded mass the size of a hen's egg below the right clavicle, and one a short distance below the left breast. A large mass of glands similar to those in the neck is to be felt in the left axilla, and a few in the right. There are also a few small glands in both groins. *Chest:* Heart normal. *Lungs:* Dullness and fine rales at the right apex. *Liver:* Normal. *Spleen:* Not enlarged. An ill-defined-resisting area can be felt above and to the right of the umbilicus.

On December 3 the glands on both sides of the neck and those of the right axilla were removed. On December 18 one thousand cubic centimeters of clear fluid was withdrawn from the right pleural cavity. This returned and approximately the same amount was withdrawn on January 2 and 18, March 7, and April 1. February 3 she was suffering considerable dyspnea and cough, and the glands had recurred on both sides of the neck. There was also an indefinite area of dullness under the sternum at the base of the heart, and an indefinite, slightly tender mass could be felt in the right iliac fossa. She died suddenly April 6, 1903, with dyspnea, cyanosis, and some exophthalmia.

No autopsy was allowed.

The temperature was very irregular, between normal and 103.

Pulse, respiration, and urine normal.

BLOOD. — Nov. 24, 1902.

Polymorphonuclear neutrophiles	80 per cent.
Basophiles	14 "
Oxyphiles	1 "

February, 1903. Hemoglobin, 85 per cent. Reds, 4,840,000. Whites, 16,000.

Polymorphonuclear neutrophiles	86.5 per cent.
Basophiles	12.5 "
Oxyphiles	1.0 "

Pathological examination of the glands removed from the neck. — The specimen consisted of a mass of lymph glands, in the aggregate about the size of the fist, with definite capsules and loosely bound together with fibrous tissue. On section, they were firm, bulging, of a grayish color, and traversed in places by fine fibrous trabeculæ.

Microscopic examination of a gland one centimeter in diameter showed no markings of a normal lymph gland. The reticulum was considerably increased, and the lymph spaces were filled with cells. Lymphoid cells of the larger and smaller forms constituted about one-half of those present, the greater part of the others having large, irregular, vesicular nuclei, and a small amount of protoplasm. These epithelioid cells were present in great numbers everywhere in the specimen, and many giant cells were seen, some with large and others with much smaller nuclei. There were many vessels. Eosinophiles were present in the tissue and in the vessels. Section from a gland eight centimeters in diameter presented the same appearance as the other, with the exception that a larger number of eosinophiles were present both in the vessels and in the tissue.

Inoculation. — Two guinea-pigs and a rabbit were inoculated December 3 with portions of a gland. One pig died the next day of an infection with gas bacillus. The rabbit died February 15. The autopsy revealed broncho-pneumonia, but no evidence of tuberculosis could be found microscopically. The second pig was killed March 2, 1903, but the autopsy showed nothing. A pig inoculated February 4 with some of the pleural exudate was killed April 9, and the autopsy revealed no signs of tuberculosis.

Case IX. — Dr. C. L. Scudder. Male, 18, single. Feb. 10, 1903.

Children's diseases, otherwise always well. Six months ago noticed a swelling over the cartilage of the second rib on the left, which has gradually increased in size to the present time. No pain or tenderness, and no constitutional symptoms.

Physical Examination. — Well-developed and nourished. No glands in neck, axillæ, or groins. *Heart* and *Lungs* normal with the exception of an area of diminished resonance anteriorally over the base of the heart extending up to the sternum and one-half inch to the right to 2.5 inches to the left of that bone. An indefinite mass could be felt at the sternal notch. Over the cartilage of the second rib was a soft tumor about two inches in diameter, not tender or painful. *Spleen* : Not enlarged.

Urine, pulse, respiration, and temperature normal the only time the patient was seen.

Blood. — Hemoglobin, 70 per cent.		Red, 4,720,000.	White, 23,000.
Polymorphonuclear neutrophiles			84.4 per cent.
Basophiles	large		5.0 "
	small		7.0 "
Oxyphiles			2.0 "
Mast cells			1.0 "

An incision was made into the tumor over the sternum and its contents curetted out.

Pathological Examination. — The specimen consisted of several small, irregular bits of yellow, necrotic-looking material and muscle with which the growth appeared to be infiltrating.

Microscopic Examination. — The specimen was for the greater part more or less necrotic, but in the better preserved places the reticulum was increased. The most striking thing was the number of eosinophilic leucocytes present which, in many fields, constituted about one-half the cells. The others were lymphocytes and large cells with irregular vesicular nuclei. Many giant cells with vesicular nuclei irregularly placed were also present. Many forms of degenerated cells were seen, and most of the fields showed a few leucocytes. Vessels were fairly abundant. (Plate XVI., Fig. 2.)

A guinea-pig was inoculated subcutaneously with a bit of the tumor on February 10, and died of unknown cause February 26. An autopsy showed an abscess at the seat of inoculation and hyperplastic glands in both groins. No tubercle bacilli could be demonstrated microscopically.

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DESCRIPTION OF PLATES.

The plates are photographs of drawings. The drawings were made by Miss Florence Byrns, the photographs by Mr. L. S. Brown.

Plate XV.

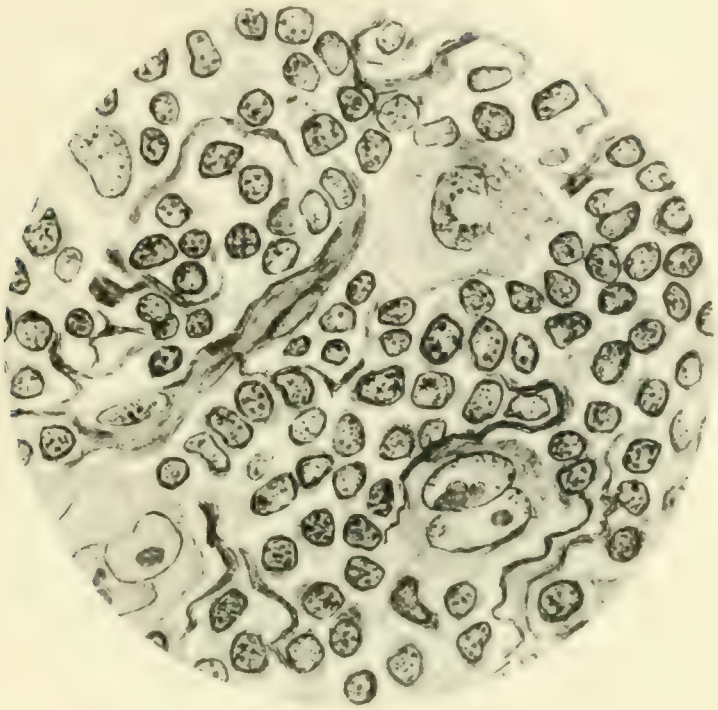
Fig. 1. — Section of gland from the neck of Case II., showing the cellular stage of the disease. The cells present are the lymphoid and the large epithelioid type. The reticulum is increased. X 550.

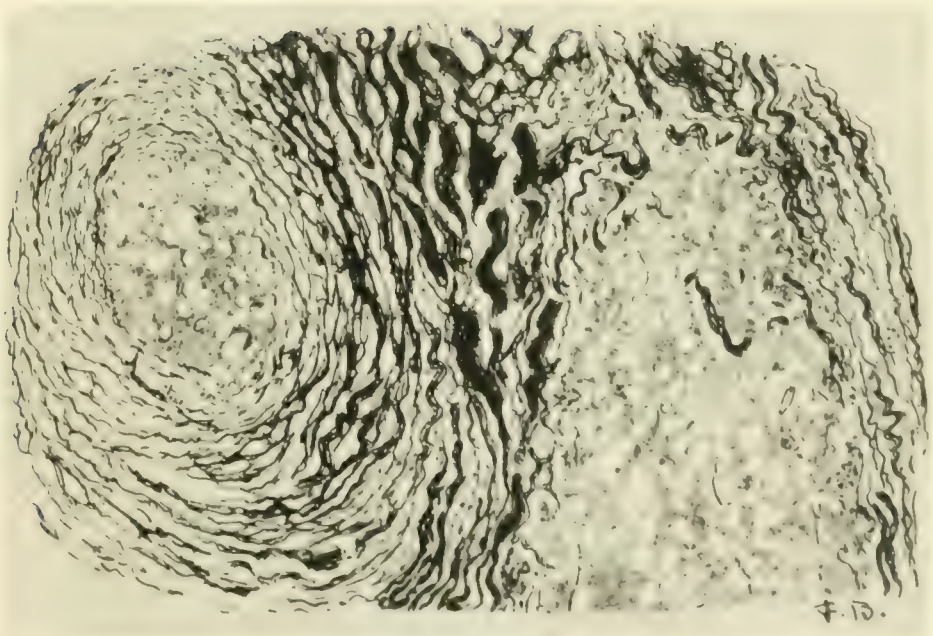
Fig. 2. — Section of the gland from the axilla, Case VI., showing the fibrous stage of the disease. Small cellular islands separated by fibrous tissue. X 40.

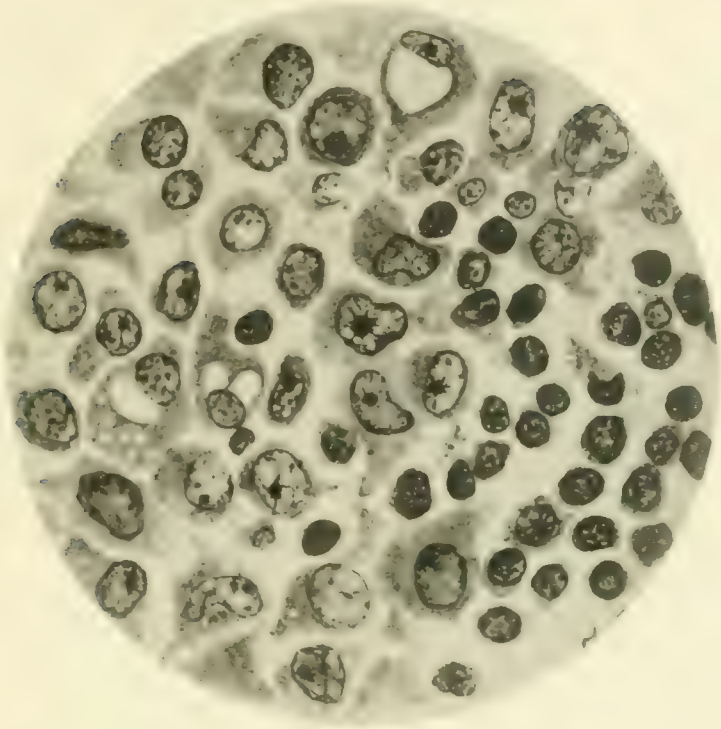
Plate XVI.

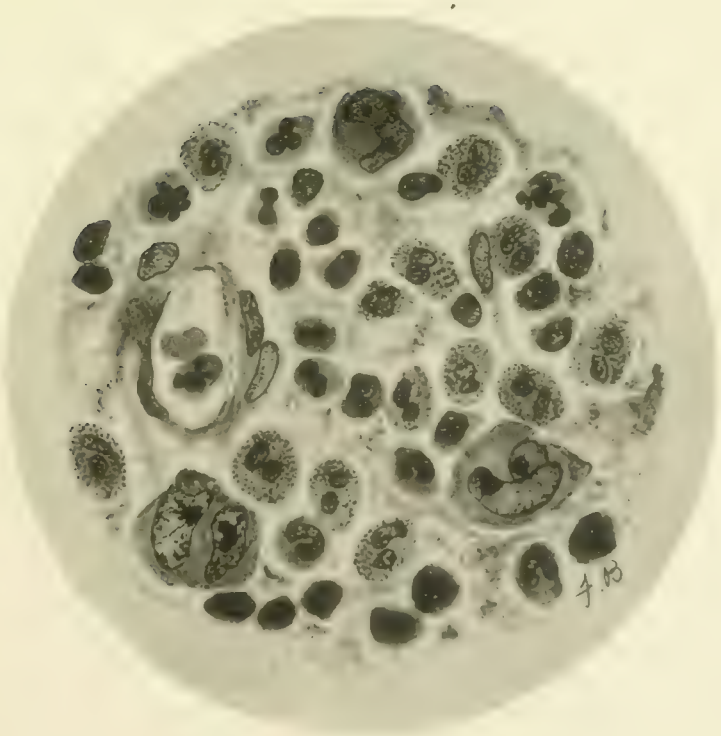
Fig. 1. — Section from a post-peritoneal gland of Case IV., showing the types of epithelioid cells. X 550.

Fig. 2. — Section from Case IX., showing the marked infiltration with eosinophilic leucocytes. X 550.









OBSERVATIONS ON THE DISTRIBUTION AND CULTURE OF THE CHANCROID BACILLUS.

LINCOLN DAVIS, M.D.

(*From the Clinico-Pathological Laboratory of the Massachusetts General Hospital.*)

(*For the Division of Surgery of the Medical School of Harvard University.*)

Ducrey[1] in 1889 first recognized and accurately described a bacillus which he found with great frequency in the pus of soft chancres. He failed to cultivate the organism on artificial media, but succeeded in obtaining it in a pure state in typical lesions in man, by successive inoculations of the pus. On this ground he based his belief that it was the specific cause of chancroid.

Soon afterwards these results were confirmed by Krefting,[2] who furthermore found the organism in the pus of buboes.

Unna,[3] a little later, demonstrated in sections of the tissue of soft chancres a similar bacillus occurring in long chains which he found constantly in the lesions, and which he called the strepto-bacillus of soft chancre.

Further investigations by Petersen,[4] Nicolle,[5] Cheinisse,[6] and others established the identity of the organisms of Ducrey and Unna. At the present time there is general agreement among bacteriologists upon the following points: Bacilli about 1.5 μ in length and 0.5 μ in thickness, with rounded, deep-staining ends, and a fainter staining central portion, occur with great constancy in the pus of chancroidal ulcerations, and less frequently in the pus of chancroidal buboes. These bacilli are found both singly and in masses, usually outside the pus cells, though sometimes within them. They occur also in very characteristic chains. In the tissues of excised chancroids the organisms are usually solid staining, and the arrangement in chains is particularly constant. They take basic aniline dyes well, but are quickly decolorized by alcohol, also by Gram's method of staining. Such bacilli have been observed hitherto in no other form of ulceration.

All attempts at cultivation of the organism prior to 1897 failed, though Petersen obtained non-characteristic growth in the depths of serum agar in one case, which failed to reproduce the disease when inoculated into man.

In 1897 Istamanoff and Akspianz[7] reported cultures in a medium of human skin and agar. The following year Lenglet[8] presented pure cultures of the bacillus of Ducrey before the French Society of Dermatology and Syphilography. The medium used was rather vaguely described as consisting of the proteid elements of human skin subjected to the action of certain energetic soluble ferments.

Inoculation of the pure culture into man reproduced the lesions, from which in turn new pure cultures were obtained.

Sections made of the artificially reproduced lesions showed chains of the bacilli in the tissues. Upon his special media the organisms grew out in long chains, the individual elements of which corresponded exactly in morphology and staining reaction to the well-recognized bacilli of Ducrey seen in the pus and tissues. No growth could be obtained in ordinary culture media. All attempts to reproduce the disease in animals failed.

In January, 1901, the convincing work of Bezançon, Griffon, and Le Sourd[9] upon the cultivation of the bacillus of Ducrey was published. These observers obtained pure cultures in four cases, two from chancroidal buboes opened under aseptic conditions, and two from extra-genital chancroids. Of the latter, one was the result of auto-inoculation from a genital lesion upon the thigh; the other was an artificial inoculation from a genital lesion upon the abdomen. The culture medium used was rabbit's blood agar in a proportion of one-third blood to two-thirds agar; also uncoagulated rabbit's blood serum. The colonies were described as appearing at the end of twenty-four hours, on the solid media, as bright, round globules which attained their complete development in forty-eight hours, becoming then opaque and grayish. They were one to two millimeters in diameter, and never became confluent. When stained and examined they were found to be composed of bacilli grouped

in masses or arranged in short chains of three or four elements. In morphology these bacilli corresponded to the descriptions of the organisms of Ducrey and Unna. In the water of condensation the bacilli were found arranged in long sinuous chains in which the individual elements were smaller than in the surface colonies.

The growth of the bacilli was equally good in rabbit's blood serum uncoagulated. Their vitality in this medium, however, was short, while on the blood agar it exceeded three weeks. All attempts at cultivation on ordinary media failed, even after acclimation through a series of tubes of blood agar. Typical chancroidal lesions were reproduced in man by inoculation from pure cultures on three occasions. From these chancroids of inoculation the organism was recovered in pure culture. Animal inoculations were in all cases negative. Monkeys were not used.

This work of Bezançon and others has since been confirmed by Simon,[10] and very recently by Tomaszewski[17] in a small number of cases.

Nicolle[11] was the first to produce the disease in animals by inoculation of chancroidal pus. He succeeded in doing this in the year 1900 with certain species of monkeys, notably the Semnopithecus. More recently Holub, a Russian observer, has reported growth of the strepto-bacillus of Ducrey in the internal organs of various insects inoculated with chancroidal pus.

My own observation on chancroid, begun before the publication of the work of Bezançon and his co-laborers, and carried on for some time in ignorance of it, while confirmatory as to the prevalence of the Ducrey bacillus in chancroidal secretions, were negative as regards its cultivation, until media containing a considerable proportion of fresh blood, as recommended by the French observers, were employed. After a few initial failures with such media, pure cultures have latterly been obtained in eight cases.

The material made use of in these observations was available through the courtesy of the staff of the Surgical

Out-Patient Department of the Massachusetts General Hospital. One or two cases were from outside sources.*

An examination of the pus of forty cases of genital ulcerations clinically resembling chancroid was made. In thirty-two, bacilli were found corresponding exactly in morphology and staining reaction to the Ducrey bacillus — the characteristic chain arrangement occurring in ten of these. In eight cases it was impossible to positively identify the Ducrey bacillus in the varied assortment of bacteria present. As improvement in technique in taking smears and increasing familiarity with the bacillus were gained, the percentage of these negative cases diminished. The bacilli were found as the prevailing organisms in the simple ulcers, as well as in the phagedenic destructive ones, and in equal numbers proportionately; seeming to show that the virulence of the process depends largely upon the resistance of the individual, an hypothesis in accord with clinical observation. Chain arrangement was noted only in cases which were actively progressing, while the location within the cells was particularly noticeable in those which were healing.

In one case, which resembled chancroid clinically, and in which Ducrey bacilli were found, secondary symptoms of syphilis developed later; this was the only occurrence noted of mixed infection.

Sections of six genital chancroids which were excised showed Ducrey bacilli in only one. The sections were stained with Loeffler's methylene blue or Unna's blue, dehydrated and cleared in aniline oil and xylol. The difficulty experienced in dehydration and clearing without decolorization of the organisms largely explains the negative results.

Pure cultures of the Ducrey bacillus were obtained directly from the pus of primary genital chancroids in two cases. In many others there was growth of the organism in culture, which could not, however, be isolated from various contaminating bacteria. One instance of chancroidal ulcerations on

* The photograph of the extra-genital chancroid is reproduced through the kindness of Dr. E. A. Codman, in whose service at the Massachusetts General Hospital the case was treated. For valuable advice and assistance in carrying on this work I wish to express my deep obligation to Dr. J. H. Wright.

the skin of the abdomen, resulting from accidental auto-inoculation from a genital lesion, also yielded pure cultures. Pure cultures were likewise obtained from chancroidal buboes opened under aseptic conditions in two cases, and from the pus of a chronic discharging bubo in one case. In four other cases of chancroidal buboes, in which the same media were used, there was no growth of any kind. Of these seven buboes, in only two were Ducrey bacilli found in smear preparations of the pus. In two cases (I. and III.) of extragenital chancroids of the fingers, which I believe to be unique, in that there were no genital lesions, pure cultures of the same organism were obtained, — in one from the ulcer direct, in the other from the pus of an abscess secondary to ulcerations on the finger.

The cultures from these eight cases, which were without contamination from the start, were identical in every detail observed, and coincided accurately with the description of Lenglet, and Bezançon, and others.

The medium used at first was rabbit's blood agar. Tubes of two per cent agar, reaction + 1.5, were melted and mixed with fresh rabbit's blood, drawn under aseptic conditions, in the proportion of two-thirds agar to one-third blood, and slanted while in a fluid state. At a later period tubes of rabbit's blood serum uncoagulated, also rabbit's blood bouillon, one-third blood to two-thirds bouillon, were used, and gave equally satisfactory results.

By employing small tubes of freshly drawn human blood, pure cultures were obtained in several instances from genital lesions direct, without any special cleansing of the ulcerated surface. This, I believe, is the best medium for obtaining cultures from a source open to contamination, the fresh blood apparently inhibiting to a certain extent the growth of extraneous organisms.

The method of preparing the media was as follows: A needle prick is made on the extensor surface of the thumb just back of the base of the nail, the skin having been previously cleansed with soap and water and alcohol. By applying a tourniquet at base of thumb just tight enough to

obstruct the venous flow, a considerable quantity of blood may be obtained. The blood is drawn up by capillary attraction into a small glass tube, one end of which has been drawn out to a very fine caliber over the Bunsen flame, and the whole tube sterilized by the same means. When about two-tenths of a cubic centimeter of blood has flowed into the tube, its capillary end may be sealed in the flame and the other end plugged with cotton, giving a miniature culture tube. The media were frequently tested after having been twenty-four hours in the thermostat at 37° C. and found sterile in all instances. All these blood media deteriorate with age, and after two or three weeks, although sterile, they are found lacking in nutrient qualities for the Ducrey bacillus.

The first manifestation of growth of the organism, after twenty-four hours in the thermostat at 37° C., was a formation of delicate flocculi in the fluid media, or in the water of condensation of the blood agar tubes. Examination of this fluid in cover-glass preparations, under the microscope, showed many chain groups made up of individual bacilli, corresponding in morphology and staining reaction to those observed in the purulent secretions. Isolated bacilli were very rarely seen. The chains in some cases were of extreme length, extending through several fields of the microscope, often in parallel lines, usually tortuous, less frequently straight, but most often tangled in the greatest confusion.

In all cultures a few long, undivided filaments were observed, often attaining a length of ten to twenty times, or more, greater than that of the individual bacillus. (Such forms were described by Lenglet also.) Transitional forms, intermediate in length and morphology between typical bacilli and the above-mentioned filaments, retaining the deeply stained rounded ends and arrangement in chains, were also observed and are shown (Fig. 13). These filamentous forms were found in both twenty-four-hour and forty-eight-hour cultures, but were far commoner in the latter, and I think are to be regarded as degenerative forms. No branching was at any time observed either in the chains or filaments.

After flooding the surface of the solid blood agar media with the water of condensation, containing a twenty-four-hour growth, small, round, grayish colonies were observed at the end of forty-eight hours. These colonies were difficult to pick up on the platinum needle, as they tended to glide in front of it. When examined under the microscope they were found to consist of the same organisms arranged in short chains and singly. The bacilli of the colonies quickly underwent involution forms, becoming misshaped and swollen and taking the stain irregularly. The same phenomena were noted in the fluid media in forty-eight to seventy-two hours. The most satisfactory stain for the bacillus in culture, as well as in the pus, was found to be carbol fuchsin followed by brief decolorization with alcohol, which brings out the bi-polar staining well. The bacilli decolorized by Gram's method as well as by mineral acids. No spore formation was observed. In hanging-drop preparations no motility could be made out. The vitality of the cultures was short, rarely exceeding three days, and in no case four days. In one case cultivation without contamination was carried to the eleventh generation with some diminution of luxuriance of growth, but without change in morphology; further cultivation was not attempted. Subcultures upon ordinary media repeatedly attempted in all cases were invariably negative, the media tried being coagulated ox blood serum, uncoagulated ox blood serum filtered, potato, agar, glucose agar, glycerine agar, agar with surface smeared with blood, hydrocele agar, hydrocele fluid, gelatin, bouillon, and egg albumen. Anaerobic cultures (Wright's method) on ordinary media were also negative, while abundant growth occurred on fresh blood media anaerobic by the same method.

Inoculation of ordinary laboratory animals, which previous observers had found invariably negative in many trials, was attempted only once. A guinea-pig was inoculated by rubbing in two loopfuls of a pure twenty-four-hour culture upon a scarified area on the back. A dry scab formed, which dropped off in three days without causing reaction of any kind.

A monkey of the genus Macaccus Nemestrinus, inoculated by the same method on the back, from the same culture obtained from Case I. showed at the end of eight days considerable elevation of the crust which had formed at the seat of inoculation. Upon lifting off the crust, a shallow ulceration was disclosed about four millimeters in diameter, containing a drop or two of pus.

A smear preparation made of the pus showed a few isolated bacilli corresponding to the Ducrey bacillus in morphology, lying within and outside the pus cells. No chain arrangement was seen. There were also a few large bacilli and cocci present. Cultures on rabbit's blood bouillon and blood serum were made from this pus. There was no growth in the blood serum tube. In the rabbit blood bouillon tube there was a profuse growth of bi-polar staining bacilli arranged in long chains exactly corresponding in morphology and staining reaction to those of the parent culture (Fig. 9). There was also a slight contamination with a long filamentous organism of large diameter with square ends, which was afterwards isolated in the depths of glucose agar. Subcultures upon all other ordinary media were negative. At the end of fifteen days the ulceration on the monkey's back had entirely healed. There was neither glandular enlargement nor constitutional symptoms at any time. At a later period inoculation of the same animal on two occasions with chancroidal pus containing bacilli (Case V.) resulted at the end of twelve days in the production of shallow ulcerations containing a few drops of pus. In this pus Ducrey bacilli were found on several occasions, almost in a pure state, arranged often in short chains (Fig. 5). Cultures in rabbit's blood bouillon from one of these ulcerations gave a typical pure growth of the organism (Fig. 10), in the other there was contamination with cocci. The ulcerations on the monkey pursued a mild course, and were entirely healed without treatment in three weeks.

In view of the extra-genital source of two of my cultures, it may be of interest to briefly review some statistics on this subject.

Ullman [14] has recently (June, 1902) published a collection of cases of extra-genital chancroid taken from the literature. His list comprises only what he considers authentic cases. Of these there are sixty-four, of which twenty-two occurred upon the fingers. In all of these twenty-two, genital lesions also were present. Nine cases were verified by finding Ducrey bacilli in the pus, four by positive inoculation, none by culture. It is interesting to note that in one of these cases reported by E. Lang there were multiple abscesses in the course of the lymphatics on the back of the hand, as in Case III. of my series.

Ullman also quotes some figures of O. Peterson's, which are not included in his own tables. Peterson collected nine thousand cases of soft chancre, of which 8,992 were located on the genitalia, or the perigenital regions (buttocks, groins, etc.), leaving eight of extra-genital site, of which five were upon the fingers.

Queyrat,[15] out of fifteen hundred cases seen by him at the Ricord Hospital, mentions only five cases in which the hands were affected. In four of these Ducrey bacilli were found in the pus. Genital lesions existed in all.

CLINICAL HISTORIES OF CASES FROM WHICH PURE CULTURES OF THE DUCREY BACILLUS WERE OBTAINED.

CASE I. — Dec. 28, 1902. Young man about twenty-six years of age, of previous good health, came to me with following history: Five days previously had run a splinter of wood into middle finger of right hand close to the base of nail. He immediately extracted the splinter. Four days later the finger caused him some pain and interfered with sleep that night. Examination on the next day showed a localized area of moderate swelling, redness, and tenderness about base of nail. After applying sulpho-naphthol poultices for two days, it became apparent that there was pus present, and a small incision under cocaine anesthesia evacuated about two drops of pus. An antiseptic dressing was applied. The pain continued, however; there was a daily discharge of pus, exuberant granulations sprang up through the incision, and altogether the wound presented an unsatisfactory appearance, although there was no extension of the process up the finger.

January 8. Under primary ether anesthesia, a crucial incision was made, the exuberant granulations curetted out, and the wound thoroughly irrigated with corrosive sublimate 1–1000, and packed with gauze. This

was followed by relief from pain, but the wound showed no tendency to heal; on the contrary the line of incision became ulcerated and undermined, and presented the appearance of a phagedenic ulcer with dirty grayish base, exuding yellow pus, surrounded by an area of moderate swelling without special induration. There was no visible extension along the lymphatics, but the epitrochlear gland was slightly enlarged. No axillary glands were to be felt at this time. The ulceration slowly extended during the next week, attaining the size of the thumb nail.

January 15. A smear preparation of the pus showed bacilli in large numbers indistinguishable from the Ducrey bacillus arranged as in Fig. 3, apparently without contamination. A culture on blood serum made at this time showing no growth, the diagnosis of probable extra-genital chancroid was made, although there was no genital lesion, nor had there been one previously. The wound was washed out with peroxide and corrosive twice daily, and also soaked in sulpho-naphthol at home.

For the next few days smears from the pus showed the same bacilli in large numbers. Cultures on agar agar smeared with blood and blood serum were tried repeatedly, but remained sterile in all cases.

January 17. Case seen in consultation with Dr. E. H. Nichols, who concurred in the diagnosis. The wound was now treated with crude carbolic and powdered iodoform; the process continued to extend nevertheless, burrowing under the skin, and forming a pocket below the ulceration, which contained four or five drops of pus.

January 25. Cultures made on rabbit's blood agar and ox blood serum eight hours after dressing. Guinea-pig inoculated subcutaneously with 1.5 cubic centimeters of a suspension of the pus in bouillon, there being two loopfuls of pus to three centimeters of the bouillon. Second pig inoculated with equal dose by intra-peritoneal injection. Some of the same pus planted on potato culture.

January 27. Culture tubes negative, except rabbit blood tube of January 25, which showed cloudiness in water of condensation. Examination of the water showed pure growth of typical Ducrey bacilli in chains. Sub-cultures were carried on for eleven generations from this tube until February 12.

Cultures of the same organism were also obtained from the ulceration on three subsequent occasions, January 28 and 30 and February 4, pure in the first two instances, but contaminated with cocci in the last.

The clinical appearance of the ulceration on the finger continued about the same until February 4, when after several applications of saturated permanganate of potash solution it began to clean up with diminution of the purulent discharge. Smear preparations of the pus after February 9 showed very scanty Ducrey bacilli, mostly within the leucocytes. The pus pocket, which had burrowed under the skin, closed spontaneously, healthy granulations appeared on all sides, and on February 14 the process had entirely healed. At this time the epitrochlear gland was still palpable, but not tender; small glands were also to be felt in the axilla, not tender.

The patient was last seen April 1, when he was still perfectly well, no sequelæ of any kind having developed. The etiology in this case remains obscure, although the possibility of venereal contact shortly after the injury to the finger, and three days before I saw him, is admitted by the patient.

The guinea-pig with intra-peritoneal inoculation of the pus appeared very dull and quiet for a couple of days, but afterwards seemed as well as ever. He was killed on the eighth day, but showed no lesions of any kind. The other pig showed no reaction at any time and was allowed to live. A monkey inoculated as above described with a pure twenty-four-hour culture of fifth generation from this case showed at the end of eight days a shallow ulcerative process, containing pus from which a culture of the original organism was recovered.

Case II. — Feb. 7, 1903. P. S., 25 years, laborer. One month previous had sore on penis, which is now healed, leaving small scar back of corona. In the right groin there is a painful, reddened, and tender swelling of two weeks' duration. On February 11, the bubo being fluctuant, an incision was made under aseptic conditions, and about thirty cubic centimeters of pus were evacuated. Smear preparations of this pus showed no bacteria of any kind. Cultures were made on ordinary blood serum and rabbit blood bouillon. No growth on the former, in the latter pure growth of Ducrey bacilli.

Case III. — Feb. 14, 1903. M. R., 30, tailor. About one month previously had pricked middle finger of right hand with a needle. Shortly afterwards the finger became sore, and about a week later tender swellings appeared on the back of hand and at elbow. He was treated for a time at another hospital, where incisions were made in the finger, and also on the back of hand and at elbow.

Examination at Massachusetts General Hospital clinic showed a fairly developed and nourished man, presenting on the palmar aspect of the second phalanx of middle finger of right hand a ragged ulceration with undermined edges and dirty base, about size of five-cent piece, with very little surrounding inflammation and no induration. A similar ulceration existed on the lateral aspect of the same finger. On the dorsum of the hand was another ulceration, and just above this a moderately tender fluctuating swelling. In the epitrochlear region, along the line of the brachial vessels, were four similar swellings, one of which had been opened and was discharging pus. There was no apparent lymphangitis in forearm and no tenderness or swelling. General condition excellent, temperature and pulse normal. There was no venereal disease present, and venereal contact of any kind was denied.

Small abscess on back of hand was opened under aseptic precautions. Smear preparations of the pus showed a few scattered Gram decolorizing bacilli similar to Ducrey bacilli in morphology. (Fig. 4.)

Cultures were taken on ordinary blood serum and in rabbit blood bouillon. There was no growth in the former, but a profuse growth of typical Ducrey bacilli in the latter medium. (Fig. 11.)

Under antiseptic treatment the ulcerations slowly healed, and the abscesses, after discharging profusely for a time, likewise closed up. The axillary glands became considerably enlarged and tender at one time, but later subsided without suppuration. When last seen at the end of March the patient was ready to return to work.

Case IV. — March 5, 1903. G.A., 25 years. Four weeks ago first noticed sores on penis coming on two days after coitus. Two weeks later noticed similar sores on abdomen caused by scratching pimples. Examination showed several superficial non-indurated ulcers on glans and contiguous parts of prepuce. On the skin of right groin and right hypochondrium were two small, undermined ulcerations. A few Ducrey bacilli were found in smears from ulcerations on penis; from ulcerations on skin of abdominal wall they were found in great numbers, arranged in characteristic chains. The extra-genital ulcerations were washed with hydrogen peroxide, and corrosive sublimate 1–1000, and sealed under sterile collodion dressings. Cultures were taken from the pus, which had accumulated under the dressings after twenty-four hours, in two weeks' old rabbit blood bouillon. Growth of cocci and colon bacilli were obtained; no Ducrey. On March 13 a pure growth of the latter was obtained on freshly drawn rabbit's blood from one of the abdominal ulcerations which had been cauterized with crude carbolic acid, and sealed for twenty-four hours under an aseptic dressing.

Case V. — Aug. 8, 1902. D. C., 29 years. Came to hospital with enlarged tender glands in right groin. Genital organs normal. On September 19 the glands broke down spontaneously. The resulting sinus was enlarged, and the wound dressed regularly at the hospital. On October 17 it was healed. On Feb. 14, 1903, the patient returned to the clinic with three small ulcerations on prepuce near frænum, which had appeared about five days before. The scar of bubo in right groin, which had been healed for four months, had broken down again, and there was a purulent discharge from the sinus. Smear preparations of the pus from preputial ulcers, also from discharging sinus in groin, showed numerous Ducrey bacilli. On February 28 monkey was inoculated on the skin of back with the purulent secretions from the sores on penis. On March 12 there was a well-developed ulceration on skin of monkey at seat of inoculation, from which Ducrey bacilli were recovered in pure culture as already described. (Fig. 10.)

On March 16 a pure culture of the Ducrey bacilli was obtained from the pus of the discharging bubo in rabbit's blood bouillon. (Fig. 7.)

At the end of March, when last seen, the chancroids were nearly healed; the bubo, however, was still discharging.

CASE VI. — March 9, 1903. J. H., 23 years. Doubtful history of syphilis one and a half years ago. Five weeks ago first noticed sore on penis; three weeks later a tender lump appeared in left groin.

Examination showed a phagedenic ulceration of the skin of shaft of penis, almost encircling the organ. In the left groin there was a mass of matted glands. Smear preparations of the pus from the chancroid showed abundant Ducrey bacilli in short chains. (Fig. 1.)

On March 15 the bubo was opened under ether, and considerable pus evacuated; the chancroid was curetted as well. No bacilli found in smears of the pus of bubo. No growth in rabbit's blood bouillon. Profuse growth of Ducrey bacilli obtained in the same media directly from chancroid. No growth on ordinary blood serum.

CASE VII. — M. C. Small, non-indurated ulceration on prepuce near frænum, enlarged tender glands in groin, short chains of Ducrey bacilli in smear preparations of pus from sore. On March 26 a pure growth of Ducrey bacilli were obtained in tubes of fresh human blood directly from the genital sore, without special attempt to disinfect its surface. Cultures on ordinary blood serum taken at the same time showed profuse growth of cocci.

CASE VIII. — March 27, 1903. P. A. Two weeks ago, four days after coitus, sore appeared on penis. A few days later noticed pain and swelling in right groin. Examination showed small, non-indurated ulceration just back of corona. Tender, reddened, fluctuating swelling in right groin. Smear of secretion from ulcer showed a few Gram decolorizing bacilli, resembling Ducrey in morphology, mixed with a large number of extraneous organisms. Bubo incised under aseptic conditions. A very few Ducrey bacilli found in the pus. Cultures made on blood serum and fresh human blood. No growth in former, in latter pure growth of Ducrey bacilli.

SUMMARY.

The results of this investigation contribute in some measure to the accumulating evidence of the specific agency of the bacillus of Ducrey in the causation of chancroid and its associated bubo; and I believe justify the following conclusions:

1. The organism is present in the purulent secretions of the great majority of cases of chancroid and occasionally also in the pus of buboes, and may be identified by its morphology and staining reaction, together with its inability to grow on ordinary culture media.

2. Characteristic growth of the organism in a pure state

may be obtained in suitable media from genital chancroids direct and also from chancroidal buboes in some cases. Growth is most luxuriant in a medium of fresh blood and bouillon, but unmixed human blood is the best medium for obtaining cultures from a source open to contamination.

3. Inoculation of a pure culture of the bacillus or of chancroidal pus upon the skin of a certain species of monkey reproduces the lesion, from which in turn the original organism may be recovered in culture.

4. The cultivation of the same organism in a pure state from lesions on the hands, clinically resembling chancroid, in the absence of genital lesions, indicates that chancroid may be primary upon an extra-genital site.

5. Bacteriological examination of all ulcers of this type is likely to establish in the future a greater prevalence of extra-genital chancroid than has hitherto been reported.

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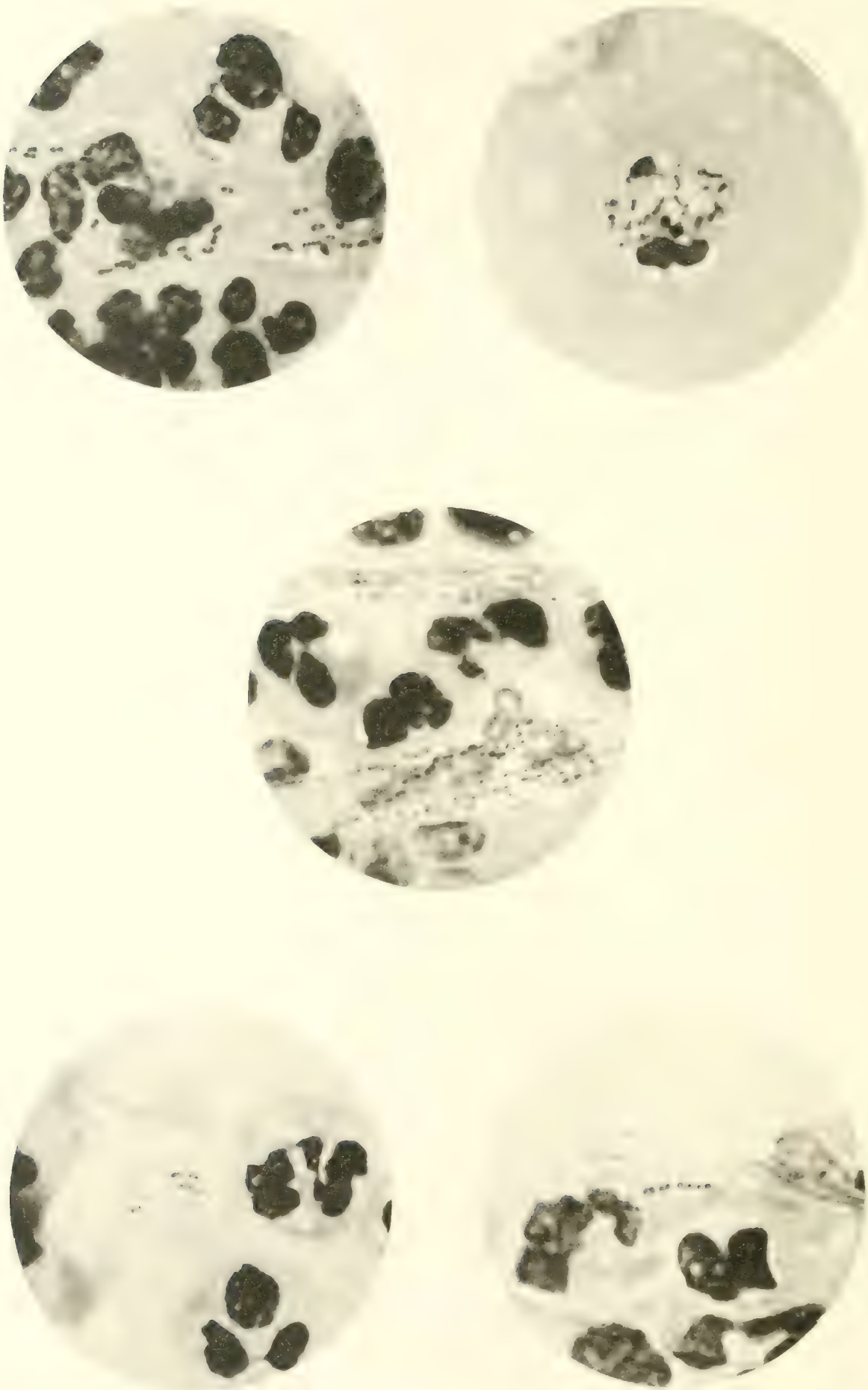

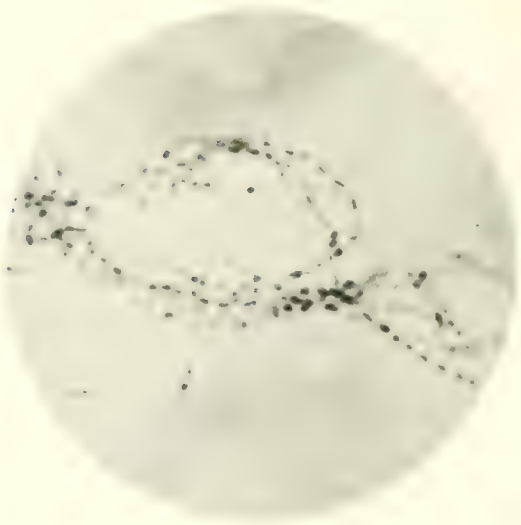

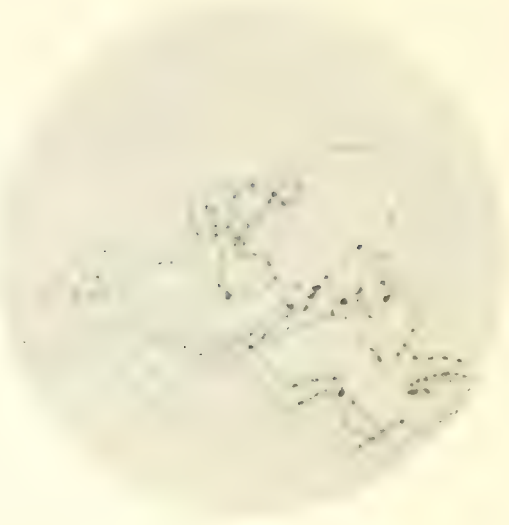

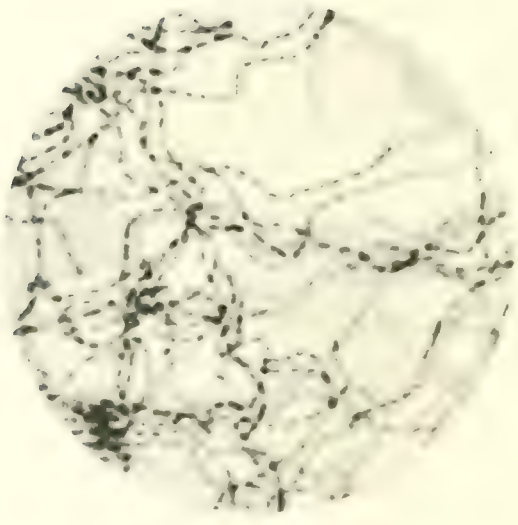

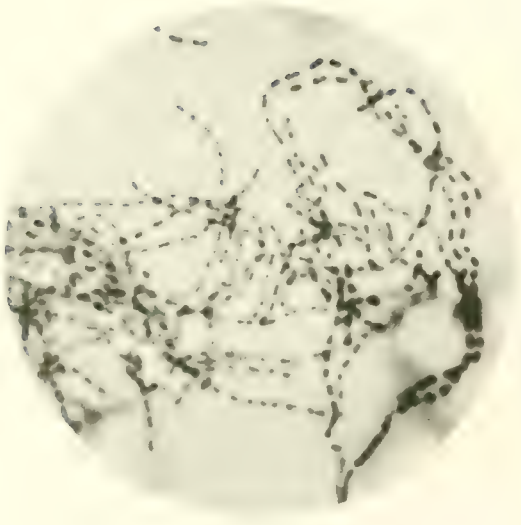

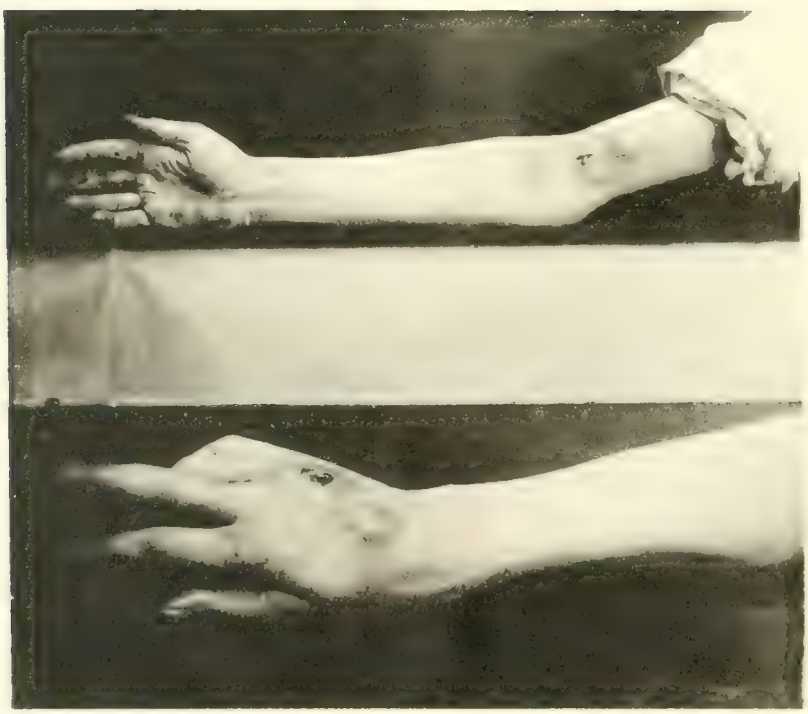

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DESCRIPTION OF PLATES.

(*Photomicrographs by Mr. L. S. Brown.*)

Both smear and culture preparations were stained with carbol-fuchsin, and briefly decolorized by alcohol. Cultures were of twenty-four hours' growth in rabbit's blood bouillon, unless otherwise specified, and were without contamination, except in Fig. 9.

Magnification one thousand five hundred diameters.

Plate XVII.

Fig. 1. Smear of pus of chancroid of penis, Case VI.

Fig. 2. Smear of pus of bubo, Case V.

Fig. 3. Smear of pus of chancroid of finger, Case I.

Fig. 4. Smear of pus of abscess secondary to chancroids of finger, Case III.

Fig. 5. Smear of pus of ulceration on monkey resulting from inoculation of pus of genital chancroid, Case V.

Plate XVIII.

Fig. 6. Culture from chancroid of penis. Medium, fresh rabbit's blood, first generation, Case VI.

Fig. 7. Culture from chancroidal bubo, second generation, Case V.

Fig. 8. Culture from chancroid of finger, third generation, Case I.

Fig. 9. Culture from ulceration on monkey resulting from inoculation of culture from Case I., first generation.

Fig. 10. Culture from ulceration on monkey resulting from inoculation of pus from genital chancroid in Case V.

Plate XIX.

Fig. 11. Culture from abscess secondary to chancroids of finger, Case III.

Fig. 12. Forty-eight-hour culture, first generation water of condensation in rabbit blood agar tube. Typical bacilli and filament, Case I.

Fig. 13. Same culture. Transitional forms.

Fig. 14. Primary ulceration on finger with secondary abscesses on back of hand and at elbow, Case III.

CHRONIC CYSTIC MASTITIS. — A STUDY OF THIRTY CASES.*

ROBERT B. GREENOUGH and HARRY F. HARTWELL.

(*From the Clinico-Pathological Laboratory of the Massachusetts General Hospital.*)

(*For the Division of Surgery of the Medical School of Harvard University.*)

The fibrous and cystic changes which occur in the female breast at about the time of the menopause have long been a matter of interest in surgery. Occurring at the time of life when malignant disease is most to be dreaded, and presenting a clinical picture which closely resembles that of cancer, these changes are of extreme importance from a diagnostic point of view. A greater significance attaches to them, however, in the minds of many surgeons because of the belief that in these involution changes occur the first steps of epithelial proliferation which ultimately lead to cancer.

Increase of the fibrous tissue and the frequent presence of cysts in the breasts of women past middle life are conditions which have been described by many writers and under many different names. Chronic Interstitial Mastitis of English writers, Chronic Cirrhosing Mastitis (Billroth[5]), Maladie Cystique de la Mammelle or Intra-acinous Cystic Epithelioma (Reclus[33]), Maladie de Reclus, Maladie Noueuse de la Mammelle (Phocas[29]), Chronic Cystic Mastitis (Koenig[20]), Periductal Mastitis (Delbet[15]), Poly-cystoma or Cyst-adenoma (Schimmelbusch[39]), Plexiform Fibroma (French writers), Cystic Disease of the Breast (Bryant[9]),

* Of the thirty cases upon which this report is based, seventeen were treated in the wards of the Massachusetts General Hospital, and were under the care of the surgeons of the staff. The remainder of the cases, thirteen in number, were obtained from the private practice of the following surgeons of this city: Drs. C. B. Porter, J. C. Warren, A. T. Cabot, M. H. Richardson, C. L. Scudder, Anna G. Richardson, H. F. Vickery, G. W. W. Brewster, and Farrar Cobb. To all of these surgeons the writers would here express their gratitude for the permission to report the cases and for the clinical details of history and treatment. To Dr. W. F. Whitney and to Dr. J. H. Wright, of the Massachusetts General Hospital, the writers feel themselves under especial obligation, not only for the generous use which they have allowed of their material, but also for much active interest and suggestive criticism during the course of the investigation.

and Fibrous Hyperplasia with Retention Cysts; all of these designations have been applied to this disease.

As may be deduced from the variety of names which have been given to this condition, different interpretations have been placed by different observers upon the pathological picture which it presents. In the main, this difference of interpretation has been influenced by the individual or even national belief of the observer, with regard to the line of division between inflammatory hyperplasia and tumor formation. In the breast, this problem presents especial difficulties, because of the intimate admixture of epithelial and connective tissue elements, and the participation of both of them in almost every pathological process, whether inflammatory or neoplastic. By the modern French school the lesions of chronic cystic mastitis are regarded as of inflammatory origin. By many German writers they are considered actual new growths and dignified by the name of Cystadenoma. Other writers take a position between these two extremes, and admit that the line of division is one which in certain cases can be drawn with difficulty or not at all. In England, especially, much has been written concerning the association between chronic mastitis and cancer. The evidence to support this relation has been derived for the most part from the examination of breasts removed for cancer which presented lesions in the breast tissue beyond the limits of the cancer growth, which were interpreted as chronic mastitis. These observations, together with the clinical evidence of the development of cancer in breasts which were previously attacked with chronic mastitis, have aroused a general distrust of the disease in England and in this country. To establish this distrust upon a more secure foundation is the object of this communication.

The technique employed in the study of the thirty cases here presented was as follows: Material from the operating rooms was examined in the fresh state, and sections were made of the entire specimen. Small pieces from many different portions of the specimen were then hardened in Zenker's fluid. After thorough washing the fixed specimens

were put through ascending alcohols and chloroform and embedded in paraffin. Sections were cut with the Minot-Blake microtome, two and three micro-millimeters in thickness, and stained with iron-hematoxylon (Mallory) and orange G. and fuchsin. Serial sections were made of tissues of special interest, and a number of other methods of staining were employed in appropriate cases. Specimens from operations in private practice were occasionally available only after fixation in formalin (5 or 10 per cent), and such specimens were as a rule inferior to the Zenker hardened ones for histological purposes.

In the study of the disease of an organ a knowledge of its normal appearances is essential. For this reason a short summary of the normal histology of the breast may here be introduced.

Shortly after puberty the female breast presents a typical picture. In a framework of interlobular connective tissue, interspersed with fat, the main ducts and the smaller lobules of the breast are widely scattered. Around each duct, and especially around each acinus, is found the cellular and delicate "periductal" connective tissue, which is peculiar to the breast. The main ducts are empty and infolded and possess a double layer of small columnar epithelial cells. The acini are small and empty, and are lined with a single or double layer of small cuboidal cells. The blood vessels are small and few in number.

With increasing age there is a slight increase in the number of the lobules, but no marked change occurs in their constituents. During pregnancy active increase takes place, not only in the number of lobules, but in the number of acini in each lobule. The gland is grossly enlarged and new blood vessels appear. The epithelium of the acini increases in development, and evidence of active growth by mitosis has been observed (Steinhaus [43]). The products of secretion are seen in the cells and filling the lumen of the acini and ducts.

During lactation the vascularity of the gland is maintained as well as the high degree of developement of acini and epithelium. Secretion products of all stages are found in the acinal epithelium and in the lumen of the acini and ducts. The acinal epithelium rarely exceeds one layer of cells in thickness at this time.

After lactation a degree of involution occurs, and the large number of acini gradually diminish. A breast which has undergone lactation rarely returns, however, to its previous condition, and a larger number of acini than in the virgin breast can generally be demonstrated. With this

diminution in the number and size of the lobules, an increase of the interlobular fibrous tissue occurs in the meshes of which the accumulation of fatty tissue is abundant.

At about the time of the menopause, between the ages of thirty-five and fifty, further involution changes take place as the functional activity of the gland is no longer required. This process occurs to the same extent as a rule in breasts which have undergone lactation and in those which have not. It consists in a further diminution in the number of glandular elements, even to the almost complete disappearance of the acini in some cases, and the formation of a dense interlobular fibrous tissue with few nuclei and with a heavy fibrillated structure. (Plate XX., Fig. 1.) The fatty tissue interspersed in the meshes of this interlobular fibrous tissue is variable in amount, and becomes gradually smaller in quantity as the fibrous tissue undergoes increase. The epithelium of the atrophic acini is small and irregular, and is disposed in one thin layer as a rule. The epithelium of the ducts is less affected, and is frequently arranged in a double layer. The peculiar periductal tissue of the breast either disappears or undergoes hyaline degeneration. The blood vessels are shrunken and few in number. This statement of the normal histology of the breast is based upon numerous specimens examined by the writers, and is controlled by the reports of similar observations by others. (Steinhaus,[43] Bizzozero and Ottolengui,[7] Warren.[46])

The thirty cases of this series presented the lesions of chronic cystic mastitis. In three the lesions of carcinoma were found in other portions of the breast, accompanying the lesions of chronic cystic mastitis. The consideration of these three cases will be deferred until after the results of the study of the simple cases have been recorded. Twenty-seven cases of uncomplicated chronic cystic mastitis presented the following clinical characteristics:

The age of the patient was stated in twenty-five cases. In sixteen cases the age was between forty and fifty years. The youngest case was twenty-five years old and the oldest fifty-two. The average being 40.4 years. This is in accordance with the view of most observers, although it shows the age incidence to be a trifle earlier than the age at which the menopause is commonly expected. The disease is therefore one which is more likely to precede the menopause than to follow it. Three cases occurred in women under thirty years of age, but the specimens in these cases presented no appreciable differences, either clinically or histologically, from those of older women.

The influence of child-birth and of lactation was not especially prominent in this series of cases. Nineteen women were married. Eight were single women. Ten of the married women had borne children; seven had borne no children, and in two cases the records were deficient. Thus, of twenty-five women suffering from this disease, ten had had children and fifteen had not. Whether or no lactation was prolonged or of brief duration, in the cases which had borne children, could not be ascertained. In a few cases the fact that lactation was present, but was suddenly interrupted, owing to the death of the child or to other considerations, has appeared to the writers to have some importance in the etiology of the disease.

An injury to the breast preceded the appearance of the trouble in only one case of the entire number. In another case infantile mastitis occurred in early life on both sides, and was followed by bilateral chronic cystic mastitis at the age of twenty-six. No case of puerperal breast abscess was noted in the entire number of cases.

Uterine disease and disorders of menstruation have been noted by several writers as accompanying this condition. Two of these cases had passed the menopause. Twelve gave a history of normal and regular menstruation, and only two cases complained of irregular and painful catamenia. When painful menstruation is present, however, it has been noted by the writers that exacerbation of the disease, with each recurring period, is even more marked than in the cases with normal menstruation. Koenig calls particular attention to this phenomenon, and attributes the increase of tenderness and even the actual increase in size of the indurated area which is occasionally noted in these cases to the congestion and tumefaction which normally occur in the breast at the time of the menstrual period.

The duration of the disease, before the patient sought medical advice, was a matter of considerable variation in this series of cases. The induration was, as a rule, discovered by the patient by chance, and a longer or shorter time elapsed between the discovery of the tumor and the seeking of medical advice, according to the state of intelligence of the patient, or the degree of anxiety which she evinced with regard to the presence of an indurated mass in her breast. Seven cases sought advice within one month after the discovery of the tumor; eight cases from one to six months after; and six cases at varying periods of time up to four years after the time when the tumor was first detected. In six cases the duration of the disease was not recorded. The shortest period elapsed between the discovery of the mass and the resort to medical advice was two days. It is evident that no deductions can be drawn from these data, with regard to the length of time the actual induration had existed.

The onset and growth of the disease in the breast was regarded as

rapid in six cases and as slow in eleven cases. Those which presented a rapid increase of size were, as a rule, the cases in which a cyst of considerable size was present and the rapid increase in size could be attributed to the collection of fluid in the cyst.

Both breasts were involved in ten cases, and only one breast in eleven cases. In six cases the condition of the other breast was not recorded. When bilateral, the disease was as a rule more marked on one side than on the other.

An induration of the breast tissue was present in every case. This induration varied from a mass, which was regarded as a tumor in ten cases, to a degree of increased consistency of the gland which was with difficulty to be appreciated. It is important in the examination of these cases, as pointed out by several writers, that the breast should be examined under the flat of the hand, and that the gland should be pressed against the chest wall, instead of being pinched up between the fingers of the examiner. When pinched up in this way a double thickness of gland tissue is felt, and the impression is readily obtained of a tumor mass not justified by an examination under the flat of the fingers. The areas of increased consistency were rarely well defined at their margins, but faded gradually into the surrounding gland tissue. When cysts of any considerable size were present, the limits of the induration were more sharply marked. In some cases an irregular "corded" feeling of the gland, with minute, more indurated spots, was all that could be detected by physical examination.

The situation of the induration in the breast was of interest. In twelve cases the disease was spread diffusely throughout the breast. In two of this number, however, the part first and most affected was the outer hemisphere. In thirteen cases the disease was localized more particularly in one portion of the breast. Of this number, eight cases showed an involvement of the outer hemisphere, two of the lower hemisphere, and two of the central portion of the breast. As in cancer, the upper and inner quadrant was the part which was most rarely affected, and the upper and outer quadrant the one most liable to attack. Where the whole breast was available for pathological examination, however, the process, though varying in extent from part to part, involved the gland as a rule in its entirety, and the apparent immunity of the upper and inner quadrant could not be substantiated.

Cysts were definitely detected on physical examination in fourteen cases. In ten cases there was doubt as to whether a cyst were present or not, and in three cases no cysts were found on gross examination of the specimen. In every case cysts were found on microscopic examination of the specimen. Two cases only showed diminution in the size of the mass from time to time. Two cases also gave the history of the discharge of a clear or watery fluid from the nipple. These symptoms, while

extremely suggestive of the presence of a cyst, as pointed out by many writers, can be considered as of only confirmatory evidence. The absence of these symptoms can have little value in diagnosis on account of the relative infrequency of their occurrence.

Pain and tenderness on palpation are symptoms of considerable importance, in connection with the generally painless character of cancer of the breast. Twelve cases complained of pain and tenderness in the breast, and seven cases gave no evidence of this condition. In eight cases the presence or absence of this symptom was not recorded.

The nipple was retracted in three cases, normal in ten, and its condition was not recorded in fourteen cases, but may be assumed to have been normal. The retraction of the nipple is not a feature of this disease, and when present is probably of antecedent origin and of negative importance.

Adherence of the gland to the overlying skin or to the underlying fascia was not found in any case.

Axillary glands of palpable size were recorded as present in seven cases. They were noted as doubtful in two and absent in thirteen cases. The examination was not recorded in five cases. When present, palpable glands were frequently found in both axillæ, whether one or both breasts were involved in the disease.

The clinical picture presented by chronic cystic mastitis may be summarized as follows: An indurated mass of irregular contour and ill-defined margins is found, either diffusely pervading the mammary gland or localized most often in the outer hemisphere. Cysts are frequently observed and may be of considerable size. The mass is generally of slow growth, unless large cysts are present. It is generally, though not invariably, painful and tender to pressure, and often involves both breasts. Discharge from the nipple and diminution in the size of the mass occur but rarely. The disease is found either in single or married women and generally at a period shortly before the time of the menopause. The skin is not adherent, and the axillary glands are but slightly if at all enlarged.

Chronic cystic mastitis is to be distinguished from the following diseases in making a differential diagnosis: cancer, sarcoma, adenoma (villous papilloma or duct cancer of the English writers), the solid and cystic fibromata (adenofibroma), galactocele and retention cysts of traumatic origin,

chronic and subacute mastitis after lactation, tuberculosis, syphilis, actinomycosis, retro-mammary disease, and foreign bodies in the breast. It is also to be distinguished from normal involution of the breast. Few of these conditions need special consideration, but attention may here be directed to the varied nomenclature employed by different writers in the description of tumors and diseases of the breast. The terminology of Gross[46] has been adopted in this paper, as being the one taught in the Surgical Department of the Harvard Medical School. By this classification the term "Fibroma" is used to denote the varied class of tumors in young adult breasts which take origin in the "periductal" tissue, and which are classed as adeno-fibromata or intracanalicular papillary fibroma by other writers. Adenoma in the Gross classification is used to indicate the tumors which present an obvious new formation of gland elements more or less typical in form, and of local character. These tumors are known as duct cancer or villous papilloma by English writers, and as proliferative or papillary cyst-adenomata in the German literature. They are of rare occurrence. Tumors of this class are with difficulty divided from certain advanced cases of chronic cystic mastitis. Papillary outgrowths of macroscopic size, such as occur in villous papilloma in the dilated ducts beneath the nipple, have been excluded from this series of cases. Such tumors almost invariably present the characteristic symptom of a bloody discharge from the nipple, and by their localized situation and limited extent can be distinguished clearly from the diffuse process in chronic cystic mastitis. Cases which present proliferative or papillary growths in the wall of a cyst can be distinguished only by the extent to which the process is judged to involve the gland. In other words, no sharp line can be drawn, either clinically or pathologically, between some cases of cyst-adenoma and chronic cystic mastitis.

The subacute and chronic suppurative processes which follow lactation are to be clearly distinguished from chronic cystic mastitis. They are accompanied by minute abscesses along the ducts, by more or less intense inflammatory reaction

in the surrounding tissues, and by their tendency to progress to suppuration. Whether or no mild degrees of this affection predispose to later cystic mastitis, as held by Delbet and others, will be discussed below.

In nine cases amputation of the breast was performed by the surgeon in charge of the case. In fifteen a portion of the gland was resected, and in two the specimen was obtained from the autopsy table. The material thus obtained was examined with reference to the following points:

The fibrous tissue was invariably increased, and generally throughout the entire gland. It was rarely homogeneously distributed, but was more dense in certain areas or about certain lobules. In twenty-six cases the process was recorded as diffuse, in only one as discrete or local. The fibrous tissue varied from white to gray in color, and in many cases was of cicatricial consistency.

Cysts were present in every case. In two cases they were of microscopic dimensions only. In twenty-five they were readily seen on gross examination. The contents of the cysts were, as a rule, fluid and varied from clear watery fluid without color, through all shades of yellow and green to dark brown and almost black. Papillary growths appreciable on gross examination were not present in any case.

Lobular proliferation without cyst formation was noted in one or two cases on gross examination, as presenting an appearance of fine granules of softer consistency scattered through the dense fibrous tissue, particularly at the outer portions of the mammary gland.

Sections made and stained by the methods already detailed were examined with the microscope, and gave the following results:

The increased fibrous tissue of chronic cystic mastitis arises chiefly, if not altogether, from the interlobular connective tissue of the gland. Every case showed increase of the interlobular tissue, while in only eight could an increase of the periductal tissue be determined, and that of only insignificant extent. The interlobular tissue was as a rule distinctly poor in cells and the fibers were broad and deeply

stained as in cicatricial tissue of an advanced age. The periductal tissue, while more cellular than the interlobular tissue, was not more cellular than in the normal breast, and in five cases marked evidence of hyaline degeneration of this tissue was apparent. In ten others slight degrees of hyaline change of the periductal tissue, especially in the portions nearest to the basement membrane of the acini, could be determined. In eleven instances hyaline changes in the interlobular tissue were observed. The distribution of the interlobular tissue was general throughout the gland, but especially surrounding the acini and ducts. Occasionally a collapsed duct was seen surrounded and apparently compressed by fibrous tissue.

Round cell infiltration is commonly regarded as evidence of an inflammatory process of a chronic nature. The same phenomenon appears, however, about a carcinoma of rapid growth, and is there attributed to the inflammatory reaction set up in the tissues as a result of the invasion of the malignant growth. Round-cell infiltration of the tissues was observed in twenty of the twenty-seven cases in this series. The situation of the infiltration was subject to a considerable degree of variation. In thirteen cases the round cells were most marked about the ducts and acini (Plate XX., Fig. 4), in five cases about the cysts (Plate XX., Fig. 3), and in two about the blood vessels. Cells of several varieties were present in this infiltration. Lymphoid cells were most frequently observed, and were present in every one of the twenty cases. Plasma cells were found in nineteen cases, and leucocytes in eight. Eosinophiles and mast cells were rarely seen. Two cases showed evidence, both clinically and pathologically, of suppuration occurring in a breast already the seat of chronic cystic mastitis. In these instances the round-cell infiltration and the presence of leucocytes were by far more marked than in the others. In several instances round-cell infiltration was most conspicuous in close proximity to the areas of most vigorous epithelial proliferation. In other cases this relation was not demonstrable. From the examination of this series of specimens

the writers were forced to conclude that the round-cell infiltration plays a secondary and subordinate part in the lesions of chronic cystic mastitis. It appears to be chiefly due to the local irritation which is caused by either degenerative or productive processes in the epithelium of the acini and cysts. This view is at variance with the greater number of the published opinions upon the subject, but in no other way can the variable and inconsequent appearance of round cells be explained. It is certain that no evidence could be found in any of this series of cases to justify the assumption of Binaud,[6] Nocard,[26] and others that a bacterial infection of the ducts is responsible for the etiology of this disease.

Endothelial cells, presumably derived from the lymph spaces, were conspicuous in three of these cases. These cells were of large size and occupied a position in the connective tissue near to the wall of cysts of considerable size. This appearance has been noted by Rogowitsch[36] and by Maly,[24] and attributed to edema and imbibition of the fluid by the cells. In our cases this explanation for the phenomenon seemed a satisfactory one, in view of the presumable blocking of lymphatics by the enlargement of the cyst.

The amount of fat in these specimens varied considerably, and seemed to depend largely upon the habit of the individual. The fat lying in the meshes of the interlobular connective tissue appeared to be diminished in sixteen cases, while in eleven no such diminution could be demonstrated. (Plate XX. Fig. 2.) The delicate fibrous tissue which enmeshed the fat cells was more cellular in character than the solid masses of fibrous tissue. It seemed possible that the increase of the interlobular fibrous tissue which occurs in this disease was, in a measure at least, at the expense of the interlobular fat and coincident with its disappearance. Interlobular fat was totally lacking in only one case of this series. Its presence, therefore, as pointed out by Rolleston,[40] would serve to distinguish this condition from the encapsulated fibromata in which no fatty tissue is found.

Blood vessels were rarely present in large numbers, and were generally small in size. Evidence of endarteritis was

very rarely seen. Few of these cases, however, were of an age to show marked senile arterial changes, and women are understood to be less liable to this disease than men.

The large ducts of the breast gland do not present marked variation in appearance in specimens of chronic cystic mastitis. Occasionally they are obviously infolded and compressed by the dense interlobular connective tissue. Often they do not show any evidence of this phenomenon. The periductal tissue of the larger ducts is normally small in amount at this stage of the breast development. The epithelium is generally two or more layers in thickness, but is ill-defined, and apparently in an atrophic condition. No evidence of proliferation, such as occurs in the adenomata which arise from this tissue, could be detected. Round-cell infiltration was occasionally present about the larger ducts, but was quite inconstant in its appearance and amount. Accumulation of degenerated epithelium and granular débris in the lumen of the larger ducts was occasionally noted.

The number of acini in each lobule was notably increased in thirteen cases and slightly increased in five. In several instances this increase was sufficient to suggest the proliferation of acini in the pregnant or lactating breast. (Plate XX., Fig. 2.) In many instances the number of acini was decidedly diminished. Variation in this respect occurred in the same breast, and even in the same section, some acini being increased and some diminished.

The peri-acinal connective tissue was never markedly increased. Occasionally it was diminished, and rarely it presented a degree of hyaline degeneration. The peri-acinal tissues, however, were frequently infiltrated with round cells, and this change, except in the two cases of suppuration, was more marked in the regions where the most increase of acini occurred, and particularly where proliferative changes in the epithelium of the acini could be demonstrated. The epithelium of the acini exhibited a great degree of variation. Where the interlobular connective tissue was greatly increased and the acini diminished in number atrophic forms of epithelium were seen. The cells were small, irregular,

flattened, and the nuclei small and with poorly staining chromatin. These regions were regarded as the unaffected portions of the gland which were undergoing normal involution.

When increase of the acini in a lobule occurred, and rarely when the number of acini in each lobule was diminished, the epithelium presented a more varied picture. One or two layers of cells were commonly found, and occasionally a more vigorous proliferation of the epithelium could be demonstrated. The cells in the proliferated areas stained well, showing a fine to coarse granular protoplasm, rarely vacuolated. The nuclei showed abundant chromatin, staining sharply as a rule, but varying somewhat from cell to cell. Mitoses were rarely observed. (Plate XXII., Fig. 1.) Between these two degrees of epithelial growth an infinite number of intermediate stages could be observed.

In the majority of instances a tendency to the formation of cystic dilatation was to be observed. No specimen of this series gave evidence of direct invasion of the connective tissue by proliferation of the epithelium of undilated acini.

Cysts obviously derived from the larger ducts could not be demonstrated in these cases. The epithelial lining of the cysts did not present the characteristics of the ductal epithelium as it is observed in adenoma derived from these tissues. The large cysts, however, in which the epithelial lining membrane had degenerated and disappeared, did not admit of any deduction with regard to their point of origin.

In the main, the cysts appeared to be derived from the smaller ducts and acini. In several cases a definite picture of the dilatation of the duct and acini of a single lobule (Plate XXI., Fig. 1) could be seen. In such cases the epithelial covering of the dilated duct was of a similar character to that of the cystic acini. For this reason a division between these two forms of cysts is impracticable, if not impossible. The dilatation of all the acini of a single lobule was observed in fifteen different specimens, and points strongly to compression of a duct as the cause of the cystic dilatation. (Plate XXI., Fig. 2.)

The epithelial lining of the cysts was subject to the greatest variation, and that without regard to the size of the individual cyst. Atrophic forms of epithelium, low cuboidal or flattened cells, with poorly staining nuclei and vacuolated protoplasm, occurred in cysts of all sizes. Epithelial cells of a normal acinal type, one or two layers deep, with well stained nuclei and finely granular protoplasm, were also found in cysts of varied sizes. Hypertrophic or proliferative epithelium of the high columnar form so frequently described in cystic disease of the breast were found in nearly every case. These cells have a coarse or fine granular protoplasm and sharply staining nuclei. They often show evidence of secretion at the extremity of the cell nearest to the lumen. They occur in cysts of all sizes, and were found in early acinal dilatation. (Plate XXII., Fig. 1.) For this reason they are regarded by the writers as derived from the acinal epithelium, rather than from the ducts. Paul[27] regards these cells as of slow growth and innocent nature. Sasse,[38] Schimmelbusch,[39] and others consider them evidence of tumor formation of the polycystoma or cyst-adenoma variety. The writers prefer to regard them as a stage of proliferation of the epithelium, the significance of which will later be discussed.

Papillary outgrowths of epithelium of this columnar form were present in thirteen cases. Papillary epithelial structures with a connective tissue stalk were produced in several instances by the confluence of two or more adjacent cysts, on the rupture of the delicate connective tissue wall between them. (Plate XX., Fig. 6.) Similar structures without a connective tissue framework were apparently produced in individual cases by the simple proliferation and heaping up of the epithelial cells. (Plate XXII., Figs. 2 and 3.)

A higher degree of epithelial proliferation in cysts was found when papillary outgrowths from the walls met and united in the center or anastomosed laterally, forming masses of epithelium without connective support. (Plate XXII., Fig. 4.) In these cell masses the tendency to the formation of a gland lumen and the arrangement of the epithelial cells radially around this space could be demonstrated beyond all

doubt. This form of growth the writers, for lack of a better term, have designated as "adenomatous proliferation." This phenomenon has been described by Paul[27] as the growth of carcinoma infiltrating a preëxisting cyst. That it approaches carcinoma is not to be denied, but in twenty-seven cases it was present seven times, and in not one of these cases could evidence of carcinoma be elsewhere obtained.

That these degrees of proliferation are progressive and lead one to another is proved by their occurrence in this series of twenty-seven cases. Twenty-four showed columnar epithelium in cysts; thirteen of these twenty-four showed papillary epithelial growth. In seven of the thirteen cases of papillary growth, "adenomatous" forms of proliferation were observed. No adenomatous proliferation occurred in cases that did not elsewhere show papillæ, and no papillæ occurred except in cases which showed columnar cells. For these reasons the writers disagree with Paul's conclusions that the hypertrophic columnar cell is an innocent and "resting" stage of the epithelium.

Evidence of active cell growth, as proved by mitoses, was present in only seven of the entire twenty-seven cases, and was found both in the cystic and acinæ types of proliferation. It must be borne in mind, however, that mitosis is a phenomenon of little negative value on account of the rapidity of the process, and that active and rapidly growing carcinomata often show only one or two mitoses, and that after the examination of many sections.

The contents of the cysts in these cases was subject to much variation. Fluid contents varied in consistency from watery to mucilaginous, and in color from colorless to green, brown, and black. Epithelial cells were frequently observed free in the cavity of the cyst. In some cases they were obviously degenerated; in other cases, well preserved and nearly filling the lumen of the cyst, fixed as it were in a coagulum of homogeneous material. Many cells showed granules of pigment, similar in every way to blood pigment; but no active hemorrhage into a cyst could be made out. Leucocytes and an occasional red corpuscle were seen; but

by far the greater number of cysts were filled with a fine granular débris which appeared to be due to the degeneration of the epithelial cells cast off from the wall of the cyst. Mention has already been made of papillary growths in cysts and adenomatous proliferation of the epithelium.

To sum up the histological changes which are found in cases of chronic cystic mastitis, the following features of the process are to be recognized:

The increase of fibrous tissue is derived from the interlobular connective tissue of the gland. It is coarsely fasciculated and of cicatricial consistency. Round cell infiltration is frequently observed, but appears to be only of secondary importance in the pathology of the disease.

The large ducts show little change in their appearance. They occasionally appear to be compressed by fibrous tissue.

The number of acini in each lobule varies considerably, and their lining epithelium is in various stages of proliferation, although rarely showing any atypical growth.

Cysts are chiefly produced by dilatation of the smaller ducts and acini. The epithelial lining is subject to the greatest variation, from epithelial cells of the normal acinal type to hypertrophic epithelium of the high columnar form. More advanced degrees of proliferation are seen in papillary outgrowths of the epithelium, with or without a connective tissue stalk. A still further stage of proliferation is seen in the formation of masses of epithelial cells in cysts by the fusion of papillary growths, and the production of cell areas of an adenomatous character.

The progressive nature of the epithelial changes in chronic cystic mastitis is a feature of the greatest importance. The nature of the cyst formation, and the part played by the epithelium in its production in this disease, has been the subject of much discussion.

Reclus[33] believed that the cyst was of epithelial origin. Koenig[20] and the modern French school[6, 15] maintain the inflammatory etiology of the disease. Schimmelbusch[39] pronounces it a tumor formation (Polycystoma). Sasse[35] gives

recognition to two classes — (*a*) Involution and inflammatory cysts; (*b*) Polycystoma.

The difficulty in drawing such a distinction as is made by Sasse is at once apparent. Every degree of variation, from simple involution to extreme proliferative cyst growth, occurs in our twenty-seven cases.

The decision of this question demands the reconsideration of several characteristics of the process, both clinical and pathological. The inflammatory and bacterial origin invoked by the modern French writers (Binaud,[6] Delbet,[15] etc.) is not supported by the histological characteristics of the tissue. Whether or not such a condition precedes the appearance of the disease cannot be authoritatively stated. No evidence exists, however, in the clinical histories to support this view.

Inflammatory changes other than bacterial in origin cannot readily be excluded in the etiology of this condition.

The main characteristic of the process by which a gland or member which is no longer of functional value to its possessor undergoes atrophy is by the disappearance of the active differentiated elements, and their replacement by fibrous tissue. This process is seen in the uterus and in the breast which undergoes normal involution.

In the breast, however, a lack of coördination between this atrophy and the fibrous tissue increase is not infrequent. Obstruction of the larger ducts by compression or by the collection in them of degenerating epithelium, and the resulting formation of retention cysts, may be considered the explanation of "involution cysts" which receives most general acceptance by German, English, and American writers.

The transition from this stage of the disease is a gradual one to the condition in which extensive proliferation of the cyst epithelium occurs, and papillary and adenomatous masses are found in the cyst cavities. The writers have been obliged to use the term "adenomatous proliferation" to describe the appearance of the epithelium in certain of these cases. The occurrence of intermediate stages, however, and particularly the widespread distribution of the adenomatous areas in different lobules of the breast, or even in both breasts,

seem to them reason sufficient to reject the term of polycystoma, or cyst-adenoma (Sasse, Schimmelbusch, Maly[24]) on account of the suggestion of a local tumor growth, which the name implies.

The epithelial proliferation in these cases is considered by the writers to be the reactionary hyperplasia of epithelium placed under abnormal conditions. It matters little whether it is classed as "adenomatous proliferation," or dignified by the name of "polycystoma." The progressive nature of the epithelial growth is the feature which must be recognized. Whether the well-known instability of the breast epithelium renders it more liable to react in this exaggerated way to causes which in other organs would not thus affect the epithelium can be only a matter of speculation. The fact is certain, however, that progressive changes in the epithelium of the breast gland are found in chronic cystic mastitis, which closely approach the border line between inflammatory hyperplasia and new growth. That these progressive changes of the epithelium occasionally go beyond this border line, and present the characteristics of actual new growth and that of a malignant nature, can be demonstrated.

Carcinoma was present, in addition to the lesions of chronic cystic mastitis, in three cases of this series. The diagnosis of carcinoma in these three cases was based upon the following histological features, which were not found in the twenty-seven cases of simple chronic cystic mastitis: (1) Extreme degrees of proliferation of the epithelium were present. (2) Irregularity in the size and shape of the epithelial cells was conspicuous. (3) Irregularity in the size and shape of the nuclei of the epithelial cells was present. (4) Mitosis was frequently observed, and the mitotic figures were occasionally atypical in form. (5) Evidence was present of the infiltration of the epithelial cells into the connective tissue stroma, in masses of irregular shape and without a limiting membrane.

The clinical features of these three cases differed in only a slight degree from those of the uncomplicated cases. One patient was forty-three years old, one thirty-nine, and one of unknown age. Two cases were married, one was

single. One of the married women had borne and nursed three children, and one was childless. No history of trauma or of breast abscess was obtainable in any case. One patient had passed the menopause, the other two gave no evidence of uterine disease or menstrual disorder. The disease had existed only from one to three months in these three cases. The progress of the disease was gradual in every case. In two cases only one breast was involved. In the other both breasts were affected at different periods.

On clinical examination the indurated area occupied the outer portion of the breast in every case, and varied in size up to a mass the size of a hen's egg. Cysts were recognized on physical examination in one case by the nodular and elastic feeling of the tumor. No diminution of size was noted in any case, but a bloody discharge from the nipple was recorded in one case. Tenderness was not observed of any marked degree in any case. The nipple was normal in appearance in all three cases. Adherence of the skin to the indurated area was noted in two cases. Palpable axillary glands were not found in any case. Two patients had the complete operation done for cancer of the breast, with amputation of the breast and dissection of the axilla. The axillary glands in one of these cases failed to show metastasis. In the other case the condition of the glands could not be determined. These two cases of amputation have given no sign of recurrence up to the present time (April, 1903), ten months in each case after the operation. The other case had the tumor resected, without removal of the entire gland, and recurrence took place three years later, in the region of the scar.

By this brief analysis of the clinical features of the three malignant cases, it is evident that no special signs or symptoms serve to distinguish with certainty between cases of simple chronic cystic mastitis and those which have progressed as far as carcinoma. Adherence of the skin to the induration and a bloody discharge from the nipple may surely be regarded as suspicious symptoms, but it would be dangerous to rely upon these two symptoms on account of the inconstancy of their appearance.

The gross examination of the specimens removed at operation in these three malignant cases failed to show positive evidence of the presence of carcinoma. They all presented the characteristic increase of fibrous tissue and multiple cyst formation of chronic cystic mastitis, and only on microscopic examination could their true nature be determined.

All three cases presented the histological appearances of chronic cystic mastitis as above described. The degree of epithelial proliferation in the cysts was, however, the most conspicuous feature of the specimens. Papillary and adenomatous types of proliferation were present in every case, similar to the degree of epithelial proliferation described in the simple cases in seven instances. In addition to these lesions, however, and as a rule in close proximity to them, were found the characteristic lesions of carcinoma above described. Numerous areas were present in each specimen in which the gradations between adenomatous proliferation and carcinoma were so delicate as to be practically indistinguishable. Only the extremes of the two conditions could with certainty be identified.

The areas of undoubted carcinoma in these specimens were all of one and the same general type. Epithelial cells of all sizes and degrees of irregularity were heaped together in masses without connective tissue support. Here and there, in the midst of the epithelial cells, spaces were found, around which the cells were placed in radial arrangement, with their long axis perpendicular to the margin of the space. Vacuoles and secretion bodies were frequently observed between the nucleus and the free border of the cell. These spaces are commonly described as the attempt of the gland cells to arrange themselves about a lumen, and carcinoma which presents this picture is commonly known as adeno-carcinoma. (Plate XXII., Fig. 5 and 6.)

Serial sections of these tissues showed in several instances that cysts with adenomatous proliferation, forming solid columns of epithelial cells, were directly continuous with acini and ducts, the lining epithelium of which was of the

high columnar type. This observation we considered definite proof that progressive changes from columnar to papillary and adenomatous proliferation of the breast epithelium occur in chronic cystic mastitis.

In other cases cell masses of similar appearance were found without relation to any ducts or acini, and were then regarded as areas of infiltration of the lymphatics by masses of carcinoma.

Round-cell infiltration was present in the three malignant cases, as well as in the simple ones. In the malignant cases the plasma and lymphoid cells, which constituted the greater part of the infiltration, were found in close proximity to the areas of most marked epithelial proliferation, and especially about the areas of undoubted carcinoma.

The relation of chronic cystic mastitis to cancer has long been a matter of discussion. Beadles[3, 4] found evidence of chronic mastitis in the breast tissue of one hundred cases of carcinoma of the breast in the outlying portions of the gland which were not involved in the tumor growth. It is not clear, however, that the lesions which he described as chronic mastitis were more than the normal involution of the declining breast. It would be futile to deny the possible coexistence of the two lesions, inasmuch as at the time of the menopause the breast is notoriously liable to both forms of disease. That chronic cystic mastitis precedes and predisposes to cancer is not thereby established. So far as schirrhus cancer is concerned, no case was found in which the lesions of chronic cystic mastitis were present during the three years which have elapsed since the first specimens for this investigation were collected. The writers can only call attention to the lack of evidence in this series of cases to justify the association of the two diseases. The relation of chronic cystic mastitis to adeno-carcinoma, on the other hand, is most conspicuous. All stages of progression between simple hyperplasia of the gland epithelium and actual adeno-carcinoma can be found. Step by step it is possible to follow the proliferation of the epithelium through the columnar and papillary forms to adenomatous proliferation and to adeno-carcinoma.

Adeno-carcinoma is generally admitted to be one of the less malignant types of cancer, and by its large bulk little danger exists of its escaping the notice of the patient until too late for operative relief. It is important, however, that its true cancerous nature be appreciated, and that the diagnosis of chronic cystic mastitis should not be allowed to quiet the apprehension of the patient, and especially of her physician.

The treatment of chronic cystic mastitis is therefore clear. Operation is indicated in almost every case, not only on account of the possible malignant tendency of the disease itself, but also on account of the entirely independent disease which its presence may mask. In certain very early cases and those with slight involvement, in which the presence of a cyst makes the diagnosis positive, delay in the application of the operation may be permissible. Increase of the indurated area, however, should be considered a positive indication for operation. The operation to be advised is the subcutaneous excision of the whole of the breast gland, leaving the nipple undisturbed. The Thomas incision below the breast makes this procedure possible with the minimum of deformity. When adenomatous proliferation is found on microscopic examination of the specimen, the case is to be regarded as one of extreme gravity, and frequent examinations by the surgeon are demanded, to ensure the early detection of a possible recurrence.

CONCLUSIONS.

1. The name of "Chronic Cystic Mastitis" (Koenig) is the most satisfactory of the many terms used to describe the condition of fibrous tissue increase and cyst formation in the female breast at the time of the menopause.

2. The use of the term "mastitis" should not imply an inflammatory process due to bacterial infection, but rather an increase of fibrous tissue of other than local tumor origin.

3. Increase of the fibrous tissue of the breast is the normal condition in the stage of decline of the gland at the time of the menopause.

4. The formation of cysts and the proliferation of the epithelium of the cysts and acini are the striking features of the disease.

5. Variations of the epithelium are found in this disease, from atrophic forms, through columnar cells, to papillary proliferation and cell masses of an adenomatous type.

6. The transition of adenomatous types of proliferation to carcinoma of the adeno-carcinoma type occurs in a limited number of cases.

7. Transition to other types of cancer was not observed.

8. The danger of the transition of chronic cystic mastitis to adeno-carcinoma is sufficient to make the removal of the entire gland advisable in all but very early and slight degrees of the affection.

9. The operation to be advised is as a rule the subcutaneous resection of the entire gland without removal of the nipple. This is best effected by means of the Thomas incision under the fold of the breast.

SUMMARY OF CASES.

CASE I. — M.G.H., Dr. Codman, 47, married, one child, three weeks, both breasts — left breast lower outer quadrant, right breast lower inner quadrant, cystic, tender. Operation, resection of cysts and indurated areas in both breasts. No recurrence one and one-half years.

Pathology: Cysts, columnar proliferation, increase of acini in few lobules, lobular cyst formation.

CASE II. — M.G.H., Dr. Warren, 45, married, four children, two years, induration size hen's egg in upper outer quadrant of one breast, slightly tender, one small axillary gland. Operation, resection. No recurrence one and one-quarter years.

Pathology: Cysts, columnar proliferation, proliferation of acinal epithelium.

CASE III. — M.G.H., Dr. Warren, 45, single, five months, induration outer lower quadrant left breast (right breast subsequently affected), cystic, not tender, nipple retracted, axillary glands enlarged. Operation resection and removal of axillary glands. No recurrence one and one-quarter years.

Pathology: Cysts, columnar, papillary, and adenomatous proliferation; increase of acini in lobules, acinal proliferation. Glands from axilla not involved. Lobular dilatation.

CASE IV. — M.G.H., Dr. Porter, 41, married, three children, two

miscarriages, two months, "tumor" in outer half of breast, tender, nipple inverted, yellow discharge from nipple. Amputation, no recurrence one and one-quarter years.

Pathology: Cysts, columnar proliferation, lobular dilatation, increase of acini in lobule, acinal proliferation.

CASE V. — M.G.H., Dr. Beach, 42, married, five months, mass size egg in upper outer quadrant left breast, not tender, cystic. Amputation, no recurrence one and one-quarter years.

Pathology: Cysts, columnar, papillary, and adenomatous proliferation, lobular dilatation.

CASE VI. — M.G.H., Dr. Warren, 37, married, no children, five months, nodular indurations in both breasts, noted diminution in size after onset, not tender, small gland in axilla. Operation, resection of indurated mass in right breast, and removal of axillary gland. Subsequent history unknown.

Pathology: Small cysts, no proliferation in cysts, slight increase acini in lobule, slight lobular proliferation.

CASE VII. — M.G.H., Dr. Conant, 49, married, two children, four months, "tumor" in left breast size silver dollar (right breast previously affected), not tender. Amputation, no recurrence in left breast, right breast recurrence of cyst formation one and three-quarters years.

Pathology: Cysts, lobular dilatation, columnar proliferation. Increase of acini in lobule. Lobular proliferation.

CASE VIII. — M.G.H., Dr. Conant, 43, married children (?), one week, nodular thickening both breasts, most in left, cystic, slightly tender, operation resection, both sides. No recurrence one and three-quarters years.

Pathology: Cysts, columnar proliferation.

CASE IX. — M.G.H., Dr. Conant, 35, single, duration unknown, mass lower half left breast, cystic (?), right breast also affected. Operation, resection of left breast. No recurrence one and one-half years in left. Induration in right breast increasing and obviously cystic.

Pathology: Cysts, columnar, papillary, and adenomatous proliferation, increase of acini in lobule, acinal proliferation.

CASE X. — Private case, Dr. Warren, 40, single, ten weeks, mass upper outer quadrant left breast, cystic, not tender, right breast similar trouble, resected four months before. Operation, resection of indurated mass. No recurrence three years.

Pathology: Cysts, columnar, papillary, and adenomatous proliferation, increase of acini in lobule, lobular dilatation, acinal proliferation.

CASE XI. — Private case, Dr. Cobb, 48, married, two children, two weeks, tender, indurated mass left breast, "tumor," right breast normal. Operation, amputation. No recurrence one year.

Pathology: Cysts, columnar proliferation, acinal proliferation.

Case XII. — Private case, Dr. Anna Richardson, 42, single, two weeks, mass upper outer quadrant right breast, nodular, not tender. Left breast, similar process less extensive. Operation, resection right breast. Subsequent history unknown.

Pathology: Cysts, lobular dilatation, columnar, papillary, and adenomatous proliferation, acinal proliferation.

Case XIII. — Autopsy case, death from cancer of uterus, 47, married, one child. No clinical history.

Pathology: Cysts, lobular dilatation, columnar, papillary, and adenomatous proliferation, slight increase of acini in lobule, acinal proliferation.

Case XIV. — M.G.H., Dr. Elliott, 32, single, five weeks, mass size egg upper outer quadrant left breast, cystic, tender. Operation, excision. Subsequent history unknown.

Pathology: Cysts, increase of acini in lobule, acinal proliferation.

Case XV. — M.G.H., autopsy case, 32, married, four children, lactation interrupted, death from pericarditis, no clinical history.

Pathology: Cysts, columnar and papillary proliferation, increase of acini in lobule, acinal proliferation.

Case XVI. — Private case, Dr. M. H. Richardson, 48, married, three children, duration (?), large inflammatory mass, cystic and suppurative. Operation, amputation. Subsequent history unknown.

Pathology: Cysts, low columnar proliferation, a case of extensive suppuration in a previously cystic breast.

Case XVII. — Private case, Dr. Warren, 48, married, no children, irregular catamenia, two days' duration, hard mass upper outer quadrant, cystic, tender, "tumor." Operation resection of indurated area. No recurrence one year.

Pathology: Cysts, columnar proliferation, lobular dilatation, acinal proliferation.

Case XVIII. — Private case, Dr. M. H. Richardson, 45, married, no children, two miscarriages, one year, mass size egg, right breast, cystic. Amputation. Subsequent history unknown.

Pathology: Cysts, lobular dilatation, columnar and papillary proliferation, increase of acini in lobule, acinal proliferation.

Case XIX. — Private case, Dr. Cabot, age unknown, married, children(?), four days, indurated cystic mass in one breast. Resection. Subsequent history unknown.

Pathology: Cysts, lobular dilatation, columnar and papillary proliferation, slight increase acini in lobule, acinal proliferation.

Case XX. — M. G. H., Dr. Elliott, 26, single, irregular catamenia, three years' duration, mass size olive, lower outer quadrant left breast, cystic. Operation, resection. No recurrence one year.

Pathology: Cysts, lobular dilatation, columnar and papillary proliferation, increase of acini in lobule, acinal proliferation.

Case XXI. — M. G. H., Dr. Richardson, 25, married, no children, one week, diffuse induration left breast, tender. Operation, resection of indurated mass. No recurrence one year.

Pathology: Cysts, slight lobular dilatation, columnar proliferation, increase of acini in lobule, acinal proliferation.

Case XXII. — Private case, Dr. Warren, 45, married, no children, duration unknown, cystic tumor, size English walnut, lower outer quadrant of one breast, tender. Operation, exploratory incision, resection of indurated area. No recurrence ten months.

Pathology: Cysts, lobular dilatation, columnar, papillary, and adenomatous proliferation, increase of acini in lobule, acinal proliferation.

Case XXIII. — Private case, Dr. Brewster, 30, married, one child, four years' duration, thrown from carriage injuring right breast, swelled up immediately, subsided, and has increased intermittently since then. Right breast diffusely enlarged, indurated, tender. Operation, amputation. Subsequent history unknown.

Pathology: Microcysts, increase of acini in lobule, acinal proliferation, lobular dilatation.

Case XXIV. — Private case, Dr. Porter, past middle life, married, children, one and one-half years, diffuse induration of breast, cysts, not tender, other breast previously removed for similar trouble. Operation, excision. Subsequent history unknown.

Pathology: Cysts, lobular dilatation, columnar and papillary proliferation, acinal proliferation.

Case XXV. — Private case, Dr. Scudder, 26, single, mastitis in infancy, bilateral, left nipple retracted since infancy, diffuse induration left breast, nodular, cystic, not tender. Operation, resection. No recurrence three and one-half months. Right breast, similar affection, resected three and one-half months later.

Pathology: Cysts, lobular dilatation, columnar and papillary proliferation, slight increase of acini in lobule, acinal proliferation.

Case XXVI. — M. G. H., Dr. Warren, 52, single, menopause one year ago, four weeks, indurated mass in central portion left breast, tender, "tumor," right breast normal. Operation, resection. Subsequent history unknown.

Pathology: Cysts, columnar proliferation, suppuration in cysts.

Case XXVII. — Private case, Dr. Brewster, 40, married, two children, eight months, diffuse induration of right breast, clear, watery discharge from nipple. Operation, amputation. Subsequent history unknown.

Pathology: Microcysts, columnar proliferation, increase of acini in lobule, acinal proliferation.

Case XXVIII. — M. G. H., Dr. Harrington, 43, married, three children, two months, nodule size walnut, outer half left breast, slightly

tender. Operation, excision. Recurrence three years. Right breast also affected.

Pathology: Cysts, columnar, papillary, and adenomatous proliferation, and adeno-carcinoma.

CASE XXIX. — Private case, Dr. Vickery, age unknown, single, one month, indurated mass lower outer quadrant right breast, cystic, not tender, adherent to skin. Operation, amputation. No recurrence ten months.

Pathology: Cysts, columnar, papillary and adenomatous proliferation and adeno-carcinoma.

CASE XXX. — M. G. H., Dr. Mixter, 39, married, no children, three months' duration, diffuse induration and nodule in upper outer quadrant left breast, tender, bloody discharge from nipple, skin adherent. Operation, excision. No recurrence ten months.

Pathology: Cysts, columnar, papillary, and adenomatous proliferation and adeno-carcinoma.

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DESCRIPTION OF PLATES.

Plate XX.

Fig. 1. Normal involution of the breast in a woman of fifty-eight years of age, from an autopsy case. Low power.

Fig. 2. Increase of acini in a lobule. Persistence of interlobular fat. Case XIX. Low power.

Fig. 3. Round-cell infiltration in the wall of a cyst. Case IV. Low power.

Fig. 4. Round-cell infiltration around a small duct, in the lumen of which exfoliated epithelium has collected, and a slight degree of proliferation has occurred. Case XXV. Low power.

Fig. 5. Involution cyst with granular contents. Case XI. Low power.

Fig. 6. Cysts derived from acini, with high columnar epithelium.

Confluence of adjacent cysts by rupture of dividing wall. Case X. Low power.

PLATE XXI.

Fig. 1. Cystic dilatation of the acini and duct of a single lobule. Case VII. Low power.

Fig. 2. Cystic dilatation of a single lobule with round cell infiltration, Case IV. Low power.

PLATE XXII.

Fig. 1. Proliferation of acinal epithelium in columnar form. Case XVIII. X 250.

Fig. 2. Proliferation of columnar epithelium of a cyst in papillary form without supporting stalk of connective tissue. Case XXIV. X 250.

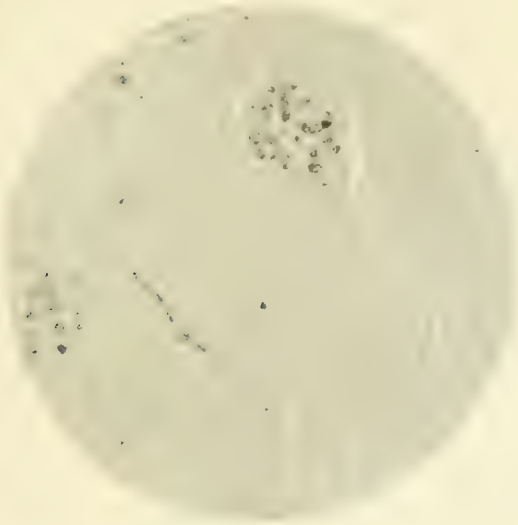
Fig. 3. Multiple acinal cysts with high columnar epithelium and extensive papillary proliferation. Case XXIV. X 125.

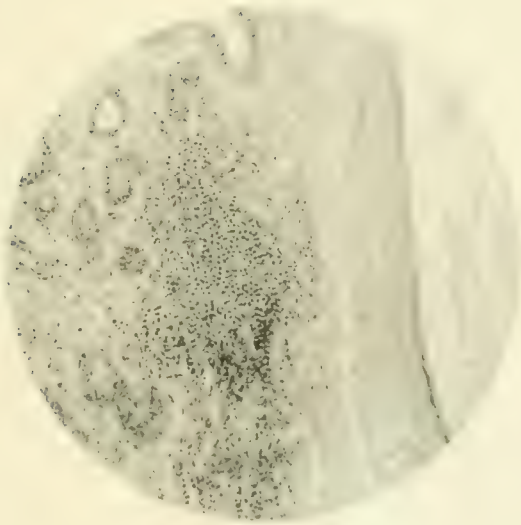
Fig. 4. Adenomatous proliferation of epithelium of a cyst. Fusion of papillary outgrowths. Case III. X 250.

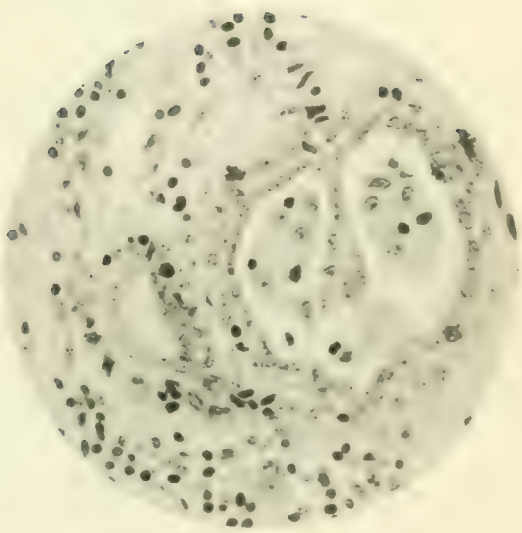
Fig. 5. Adeno-carcinoma. Masses of proliferated epithelium in the walls of cysts and forming solid bodies of cells in which gland lumina are present. Case XXVIII. Low power.

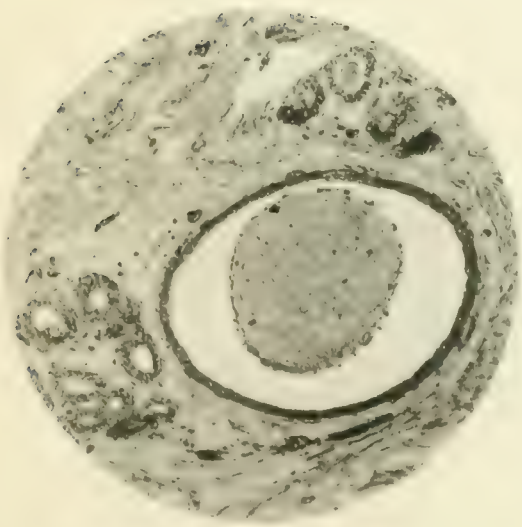
Fig. 6. Adeno-carcinoma. Masses of epithelial cells in which gland lumina are present with cells arranged radially around them. Case XXIX. X 250.

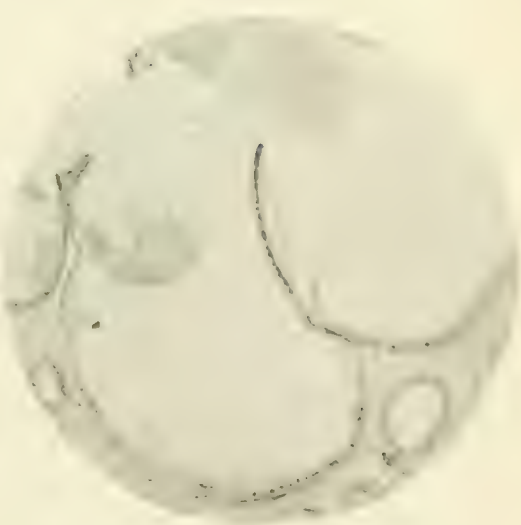
The photo-micrographs for this article were made by Mr. L. S. Brown at the Massachusetts General Hospital.











BACTERIOLOGY OF THE FIBRINOUS EXUDATE IN SEPTIC PERITONITIS.

THOMAS J. MANAHAN, M.D.

(*From the Clinico-Pathological Laboratory of the Massachusetts General Hospital.*)

(*For the Division of Surgery of the Medical School of Harvard University.*)

The presence of fibrin in acute infections of the peritoneal cavity is so frequent that it has seemed desirable to make a series of observations, in order to determine whether bacteria are present or absent in the fibrin. There is a difference of opinion among surgeons in regard to the treatment of the fibrinous exudate in operations. One group maintains that the fibrin may be left without harm, while another says it should always be removed. Finney says "the intestine should be thoroughly wiped off, in order to remove the flakes of partially organized lymph. It should be done thoroughly and conscientiously, however, as upon this, in a great measure, depends the success of the operation." (Finney, Johns Hopkins Bull., July, 1897.)

By presenting the following series of cases, I have endeavored to show that the organism causing the infection is, in most cases, present in the meshes of the fibrinous exudate.

METHOD OF EXAMINATION. — Cover glasses were taken from the fluid exudate and, in some cases, from the field of cleavage between the fibrin and the surface of the intestine. Cover glasses were then stained by Gram's method, methylene-blue, and eosin. (Smith, in Mallory and Wright's Path. Tech., p. 140.) Cultures on blood serum were taken from the same sources as the cover glasses, and from these dilutions were made. In some cases the presence of organisms of the colon group required the cultures on sugar agar. Plate cultures were also used when the variety of organisms was great. Anaerobic cultures were also made according to Wright's method. (Mallory and Wright, Path. Tech.)

METHOD OF OBTAINING THE FIBRIN. — By means of a director and a smooth-toothed forceps, the fibrin was peeled off the surface of the intestine and placed at once in ninety-five per cent alcohol. The fibrin was imbedded in paraffin by the usual method. The preparations hardened in Zenker's fluid contained so much precipitate that the sections were confusing.

METHOD OF STAINING. — Several methods were used. In some instances one stain worked to advantage, while in others it proved a failure. The following stains were found to be the most useful:

1. Carbol-thionin. (Nicolli.) (Hewlitt, Man. of Bacteriol., p. 76.)
2. Gram, eosin, methylene-blue. (Smith, Mallory and Wright, Path. Tech., p. 140.)
3. Gram and Aurantia, two per cent. (Smith.) This stain was suggested to me by Dr. W. H. Smith.
4. Carbol-fuchsin and Gram. (Flexner, Johns Hopkins Bull.)
5. Carbol-thionin and Gram. (Hewlitt, Man. of Bacteriol., p. 80.)

Nineteen cases of acute septic peritonitis were available for the purposes of this investigation. The clinical and pathological features of these cases were as follows:

CASE I. — *History:* Cancer of rectum, seven months' duration. Operation, inguinal colotomy. Second operation, nine days later. Resection of coccyx, with excision of rectum and lower end of sigmoid flexure.

Autopsy: General fibrino-purulent peritonitis. A portion of the remaining part of the rectum presented a dirty-gray appearance. It was destitute of mucous membrane and of a large portion of the muscularis. No perforation was found.

Smear preparation: Innumerable streptococci, leucocytes, and shreds of fibrin were found. Non-Gram-staining small bacilli.

Cultures on blood serum and sugar agar showed streptococci and a bacillus of the colon group.

Microscopic examination of fibrin and of peritoneum shows complete necrosis of the tissues, with no cell elements remaining. Innumerable

streptococci and a great variety of bacilli. Sections were stained by Gram's method, eosin and methylene blue, also by Gram's method and Aurantia. Plate XXIII., Figs. IV. and V.

CASE II. — Man, aged 42. *History:* Acute abdominal symptoms thirty-six hours before operation. Leucocytosis, 14,000. Diagnosis, appendicitis. Operation, abdominal cavity contained a small quantity of yellowish-brown fluid. Culture from this fluid was sterile. Appendix: Free surface injected and rough. Mesentery thickened. Second incision was made at the outer border of the left rectus, and the bowel accidentally punctured. The intestinal wound was closed with Lembert sutures, and the abdominal cavity closed without drainage. Death on the third day after operation. Symptoms of peritonitis appeared twelve hours after operation.

Autopsy: Acute fibrino-purulent peritonitis. Pelvic cavity contained a slight amount of reddish fluid. Serosa of the liver markedly injected. An adherent, fibrinous, reddish material is present along the coils of the intestine, and is very adherent in the lower abdomen. In the pelvis, distinct patches of different fibrinous material are present.

Smear preparation: Leucocytes. Vast number of bacteria, among which are a few micrococci.

Cultures on blood serum and sugar agar show bacilli of the colon group.

Fibrin: Granular fibrillæ. Leucocytes and several medium-sized bacilli. These sections were hardened in formalin and stained with carbol-thionin.

CASE III. — Woman, aged 31. Operation for increasing symptoms of intestinal obstruction of five weeks' duration. No evidence of peritonitis found at operation. Second operation the following day. Mixter tube placed in the jejunum. Death on the third day.

Autopsy: General peritonitis. No free fluid. Intestines injected. Dark and dull on the surface, with adherent fibrinous shreds.

Smear preparation: Many leucocytes, some lymphocytes, and endothelial cells. Many large Gram-staining capsulated bacilli. Morphologically this organism is considered to be the Bacillus aerogenes capsulatus of Welch. Also a large number of small, non-Gram-staining bacilli and a few short chains of streptococci.

Cultures from the peritoneal cavity on blood serum and sugar agar showed a small bacillus of the colon group. No anaerobic culture made.

Fibrin: Fibrillæ, leucocytes, and plasma cells. Several large capsulated Gram-staining bacilli.

CASE IV. — Woman, aged 56. *History:* Acute abdominal symptoms of eight days' duration. Patient was moribund on reaching the hospital, and no operation was performed. Leucocytosis, 38,000.

Autopsy: Gangrenous appendicitis. Diffuse fibrino-purulent peritonitis. The distal portion of the appendix is gangrenous, and has sloughed off. The abdominal cavity contained about 200 cc. of dirty brown opaque

fluid. Fibrinous adhesions between the coils of intestine. In other places the intestine was covered with a fibrinous exudate.

Smear preparation: Leucocytes. Many large capsulated bacilli, Gram-staining. Several small, non-Gram-staining, capsulated bacilli, few streptococci.

Cultures on blood serum and sugar agar showed bacilli of the colon group.

Fibrin: Sections were stained by Gram's method and Aurantia, thionin, methylene blue and eosin, and Gram's method, methylene blue and eosin. Fibrillæ, leucocytes, plasma, and endothelial cells. Marked fragmentation. Many large Gram-staining bacilli morphologically like the B. aerogenes capsulatus of Welch. Several smaller non-Gram-staining bacilli. Plate XXIII., Figs. I. and II.

Case V. — Woman, aged 30. Operation, laparotomy. In the mesentery of the small intestine several enlarged glands were found, varying in size from a chestnut to a large hazelnut. Microscopic examination of a portion of one of these glands showed tuberculosis. Several of these glands were shelled out of the mesentery. The abdominal wound was closed without drainage. Symptoms of peritonitis began on the second day after operation. Death on the seventh day.

Autopsy: General fibrino-purulent peritonitis. Tuberculosis of the mesenteric glands. The abdominal cavity contains a considerable amount of frank yellow pus. Intestinal coils dark red, injected, and glued together by a yellow fibrino-purulent material.

Smear preparation: Leucocytes. Several short chains of streptococci. Many small, non-Gram-staining bacilli with rounded ends.

Cultures on blood serum and sugar agar show streptococci and a bacillus of the colon group.

Fibrin: Fibrillæ well developed and filled with leucocytes and many plasma cells. At the edges of the section of the fibrin are many Gram-staining micrococci and a few non-Gram-staining bacilli. The distribution of the organisms in this case differs from other cases in that the bacteria lie on the surface of the fibrin, and are not contained within the meshes.

Case VI. — Man, aged 49. Operation for partial intestinal obstruction. At the operation the duodenum was found dilated, with the small intestine collapsed below the lower end of the duodenum. The upper end of the jejunum was opened, and a stricture found. The stricture was relieved by a plastic operation, and the intestinal wound was closed with silk sutures. Symptoms of peritonitis appeared on the second day after operation. Pus appeared in the abdominal wound on the fourth day. Death on the eighth day.

Autopsy: Fibrinous peritonitis. Sutured wound at upper end of jejunum. Tuberculosis of lungs with cavity formation. The peritoneal cavity is moist, and the intestinal coils glued together by a grayish fibrinous exudate. The edges of the sutured wound in the jejunum are necrotic, and can easily be separated.

Smear preparation: Leucocytes. Non-Gram-staining bacilli and streptococci.

Cultures on blood serum and sugar agar show streptococci and a bacillus of the colon group.

Fibrin: Granular fibrillæ. Leucocytes. Considerable fragmentation. Few Gram-staining micrococci.

CASE VII. — Man, aged 39. *History:* Symptoms of appendicitis of ten days' duration. Operation, opening and draining a localized appendix abscess. The appendix was sloughed off at its proximal end. The wound was left open, and the abscess cavity drained. Cultures at operation showed a profuse growth of bacilli and a few streptococci. Pathological report: Gangrenous appendicitis. Death on the sixteenth day after operation.

Autopsy: General fibrino-purulent peritonitis. Peritoneal cavity contains a considerable amount of yellowish, semi-fluid, purulent material. The omentum is adherent to the intestine in places. In the meshes of the omentum and contained within adhesions are small pockets of yellow pus. Intestines in places glued together with fibrinous exudate. Some portions of the intestines are almost gangrenous. Appendix was found sloughed off.

Smear preparation: Leucocytes, streptococci, and a few, small, non-Gram-staining bacilli.

Cultures on blood serum and sugar agar showed streptococci and B. coli communis.

Fibrin: Fibrillæ, leucocytes, lymphocytes, and plasma cells. Many Gram-staining micrococci. Several small, non-Gram-staining bacilli. Cell elements few.

CASE VIII. — Woman, aged 63. *History:* Symptoms of chronic intestinal obstruction, with increasing symptoms for nine months. Three hours before operation the patient was seized with sharp abdominal pain, accompanied by vomiting. The lower part of the abdomen was distended. Operation, laparotomy. The abdominal cavity contained considerable free brownish fluid and fecal material. Intestines shiny, but injected. No fibrin on the intestines. A minute opening was found in the cecum two inches above the appendix. This opening was closed by a purse-string suture, and a Mixter tube was placed in the descending colon. The abdominal cavity was flushed out with salt solution. Pelvis and both flanks were drained. Death two hours after operation.

Autopsy: General fibrino-purulent peritonitis. Adeno-carcinoma of the transverse colon, with metastases of the liver. Large and deep ulcers on the ileum and cecum. The peritoneal cavity contains a moderate amount of putrid fluid, and the coils of the intestine are weakly adherent. In places there are patches of fibrino-purulent material.

Smear preparation: Leucocytes. Many bacilli of different diameters, the majority non-Gram-staining. Several large Gram-staining bacilli.

Cultures on blood serum and sugar agar showed B. coli communis.

Fibrin: Fibrillæ, many leucocytes. Several non-Gram-staining, small bacilli; few Gram-staining micrococci.

CASE IX. — Woman, aged 37. *History:* acute abdominal symptoms three days before death. Miscarriage on the second day. No operation.

Autopsy: General fibrino-purulent peritonitis. Pneumococcus septicemia. Peritoneal cavity contains a large amount of thick, yellowish, purulent material, supporting much shaggy fibrinous exudate. Intestines, liver, and spleen are almost completely covered with a thick, fibrinous exudate. Uterus and tubes show no evidence of acute infection. Cultures from heart blood show pure growth of pneumococci.

Smear preparation from peritoneal cavity: Many leucocytes. Several pneumococci free and in leucocytes.

Cultures on blood serum show pure growth of pneumococci.

Fibrin from small intestine and surface of spleen, stained by Gram's method, methylene blue, and eosin, show leucocytes, granular fibrillæ, and many pneumococci free, and contained within the leucocytes. Plate XXIV., Figs. 1 and 2.

CASE X. — Woman, aged 42. *History:* symptoms of acute abdominal infection eleven days before death. Leucocytosis varying between 42,000 and 53,000. No operation.

Autopsy: chronic purulent salpingitis. Diffuse fibrino-purulent peritotonitis. Streptococcus septicemia. Peritoneal cavity contains 300 cc. of opaque, creamy-white pus. Adherent to the serosa of the small intestine are patches of grayish-white elastic membrane which is easily removable. There are also fibrinous masses on the surface of the liver. Right Fallopian tube thickened and contained greenish-yellow pus.

Smear preparation of abdominal pus showed leucocytes and very numerous streptococci.

Culture on blood serum showed a pure growth of streptococci.

Fibrin: Leucocytes, lymphocytes, and many plasma cells. Fibrillæ distinct. Many micrococci and streptococci.

CASE XI. — Man, aged 18. *History:* typhoid fever symptoms; Widal positive eight days before operation. Ten hours before operation, sharp abdominal pain followed by falling temperature with increasing leucocytosis to 14,000. Operation, laparotomy. The lower third of the abdomen was found filled with a milky fluid. The opacity of the fluid was greater in the pelvis. A few small flakes of fibrin were found on the surface of the small intestine, and were removed. A perforation of the small intestine was found fourteen inches above the ileo-cecal valve. The perforation was closed with a Lembert suture of silk, and the abdominal cavity washed out with salt solution. Abdominal wound closed with drainage. Recovery.

Smear preparation: Leucocytes. No bacteria.

Cultures on blood serum showed a few colonies of bacilli of the colon group. Cultures on sugar agar produced gas.

Fibrin: Few fibrillæ. Many leucocytes and lymphocytes. No bacteria. These sections were frozen sections and were stained with carbol-thionin.

CASE XII. — Man, aged 21. *History:* Typhoid fever of nineteen days' duration. Symptoms of perforation five hours before operation. Laparotomy. On opening the peritoneal cavity thin milky fluid and gas escaped. There was a fibrinous exudate on the lower part of the ileum; nine inches above the ileo-cecal valve is a perforation one-fourth inch in diameter. The perforation was closed with a silk Lembert suture. Laparotomy wound closed with drainage. Death on the third day after operation. Culture taken at the operation shows numerous colonies of Staphylococcus pyogenes albus and B. coli communis.

Autopsy: General fibrino-purulent peritonitis. Multiple typhoid ulcers of ileum with two perforations. The typhoid bacillus was isolated from the spleen. The abdominal cavity contained a moderate amount of yellow, semi-purulent material. The surface of the small intestine is covered with a yellowish scummy exudate. There are also fibrinous patches on the liver and spleen. The sutured perforation had broken away at the upper end of the opening. There were also two other perforations which were not sutured.

Smear preparation: Leucocytes, streptococci, and non-Gram-staining bacilli.

Cultures on blood serum and sugar agar showed bacilli of the colon group.

Fibrin: Fibrillæ distinct. Leucocytes. The majority of the organisms are streptococci, some of which are within the cells. There are also a few short, non-Gram-staining bacilli. Plate XXIII., Fig. 3.

CASE XIII. — Woman, aged 21. *History:* Miscarriage nine days before operation. Foul brownish vaginal discharge. Operation, curetting uterus. Death on the following day.

Autopsy: Abscess of pelvis. Diffuse fibrino-purulent peritonitis. Recent abortion. The abdominal cavity contains two quarts of thin, yellow purulent fluid. The loops of the small intestine are glued together with a fibrino-purulent material. The abscess cavity in the pelvis communicates by an opening with the rectum.

Smear preparation from peritoneal exudate: Mass of bacteria of very great variety.

Culture on blood serum and sugar agar showed B. coli communis.

Fibrin; Hyalin fibrillæ distinct. Many leucocytes. Many Gram-staining micrococci. Several medium-sized, rather thick bacilli with rounded ends, Gram-staining.

Case XIV. — Woman, aged 52. *History:* Operation for cancer of uterus. Complete hysterectomy. Drainage through vaginal and abdominal wounds. Amputation of right leg for thrombo-phlebitis of right iliac vein. Death on the fifth day after laparotomy.

Autopsy: Peritoneal cavity contains a moderate amount of yellow, semi-purulent material, most marked in right iliac fossa. The coils of intestine are glued together at their margins of contact with a soft, purulent exudate. The serosa of the intestine shows considerable injection. In the posterior wall of the upper part of the rectum is an opening one cubic centimeter in diameter. The adjacent tissues are pus-laden, and these tissues are in direct relation with the pus-laden tissues in the right iliac fossa.

Smear preparation: Many leucocytes. Several small, non-Gram-staining bacilli, resembling the colon bacillus. Several slightly larger capsulated non-Gram-staining bacilli.

Cultures on blood serum and sugar agar showed B. coli communis and B. mucosus capsulatus.

Fibrin: Very few, small, non-Gram-staining bacilli. Leucocytes, lymphocytes, and plasma cells. Fibrillæ distinct. There is considerable fragmentation.

Case XV. — Man, aged 42. *History:* Failing compensation of heart. Mitral stenosis. Acute abdominal symptoms two days before death

Autopsy: General peritonitis; icterus; streptococcus septicemia. Peritoneal cavity contains a large amount of opaque yellow fluid supporting yellowish flocculi. Serosa is injected. There are flakes of fibrin on the intestine, liver, and spleen.

Smear preparation: Leucocytes, lymphocytes, and several endothelial cells. Many streptococci.

Cultures on blood serum showed a pure growth of streptococci.

Fibrin: Many leucocytes; several endothelial and plasma cells. There are also several degenerated cells which are not inconsistent with degenerated lymphocytes. Few micrococci and streptococci.

Case XVI. — Woman, aged 52. Operation, partial gastrectomy followed by end-to-end suture; drainage by wicks above and below the line of suture. Symptoms of peritonitis appeared on the fourth day after operation. Death on the eighth day.

Autopsy: General peritonitis. Open wound of stomach. Peritoneal cavity contains a moderate amount of brownish opaque fluid. There is a yellowish membranous exudate on the intestines of the upper part of the abdomen.

Smear preparation: Many leucocytes; few lymphocytes. Several large, capsulated, Gram-staining bacilli. These are regarded as B. aerogenes capsulatus. Many micrococci, Gram-staining; some in chains.

Cultures on blood serum showed streptococci, and an unknown, medium-sized, non-Gram-staining bacillus.

Fibrin: Few fibrillæ, many leucocytes, lymphocytes, and plasma cells. Several streptococci and several large, Gram-staining bacilli. Many non-Gram-staining bacilli resembling the unknown bacillus seen in the culture.

CASE XVII. — *History*: Acute abdominal symptoms eight days before death. No operation.

Autopsy: Embolism of the superior mesentery artey, with infarction of the cecum, ileum, and ascending colon. General peritonitis. Peritoneal cavity contains a small amount of opaque fluid, supporting greenish-yellow flocculi. Intestines are injected, and at the margins of contact present streaks of greenish-yellow fibrinous exudate.

Smear preparation: Many leucocytes, lymphocytes, and several endothelial cells. Many capsulated, non-Gram-staining bacilli of varying sizes. Few medium-sized Gram-staining bacilli and micrococci.

Cultures on blood serum and sugar agar showed B. coli communis and B. mucosus capsulatus.

Fibrin: Fibrillæ distinct. Leucocytes, lymphocytes, and endothelial cells. Some fragmentation. Many small, non-Gram-staining bacilli of varying sizes. Few slightly larger Gram-staining bacilli and a few short chains of streptococci.

CASE XVIII. — *History*: Intestinal obstruction from cancer of the transverse colon. Operation, resection of transverse colon, end-to-end suture drainage. On the third day after the operation the abdominal cavity was reopened. Purulent fluid escaped. The intestines were injected, and covered with fibrinous flakes. Patient died three hours after second operation. No autopsy.

Smear preparation: Leucocytes, non-Gram-staining bacilli and several streptococci.

Cultures on blood serum and sugar agar showed a profuse growth of bacilli of the colon group and streptococci.

Fibrin: Much granular material; small fibrillæ poorly developed. Many leucocytes and lymphocytes. Many micrococci, some in chains. Several non-Gram-staining bacilli of varying diameters and lengths.

CASE XIX. — Woman, aged 40. *History*: Intestinal obstruction of five days' duration. The obstruction was in the pelvis, and due to a pelvic abscess and adhesions. Operation, inguinal colotomy, with drainage of the pelvis. Culture taken at operation showed the B. mucosus capsulatus Death on the fifth day.

Autopsy: Pelvic abscess; general peritonitis. Very small amount of free fluid in the peritoneal cavity. One coil of intestine, dark gray in color, with dark red streaks along the margins of the contiguous coils.

Smear preparation: Streptococci and several non-Gram-staining capsulated bacilli.

Cultures showed streptococci and the colon bacillus.

Fibrin: Granular fibrillæ, leucocytes, lymphocytes, and several plasma cells. Numerous micrococci and bacilli at the edges on the surface of the fibrin.

Summary.

Material was collected from nineteen cases of acute peritonitis. In seventeen of these cases bacteria were found in the fibrin. In two cases organisms were present in cover glass and culture, but could not be identified in the fibrin.

In three cases (Nos. IX., X., and XV.) no lesion was found in the peritoneal cavity as a cause for the peritonitis. In one of these, Case IX., pneumococci were present in smear preparation, in culture, and in the fibrin. The duration of the infection in this case was three days.

In Cases X. and XV. streptococci alone were found in the smear preparation, culture, and fibrin. The duration of the disease in Case X. was eleven days and in Case XV., two days.

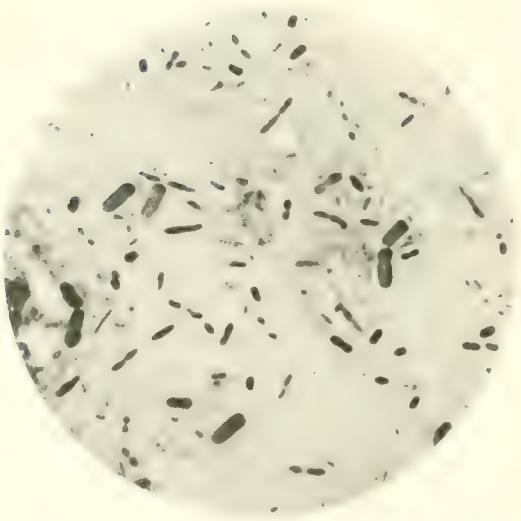
In seven cases (Nos. I., V., VI., VIII., XII., XVI., and XVIII.) streptococci and colon bacilli were present in the smear preparations, culture, and fibrin. In some of these cases, however, one of the organisms occasionally failed to be isolated in culture, although the organism was present in the smear and in the fibrin.

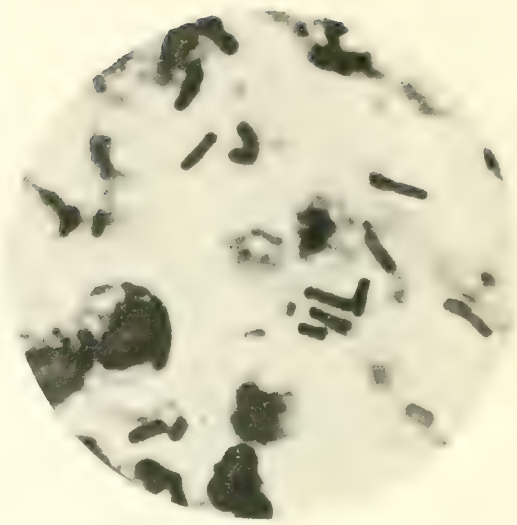
Two cases (Nos. I. and IV.) showed streptococci, colon bacilli, and B. aerogenes capsulatus. Bacillus aerogenes capsulatus was present in the smear preparation and in the fibrin in each case, but was not isolated in culture, although anaerobic cultures were made.

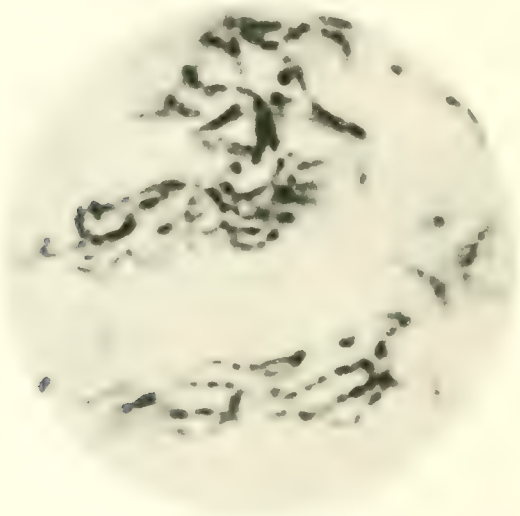
Case XIX. showed streptococci and colon bacilli in the smear preparation, in the culture, and in the fibrin. A culture in this case was taken at the operation five days before death, and showed streptococci and the B. mucosus capsulatus.

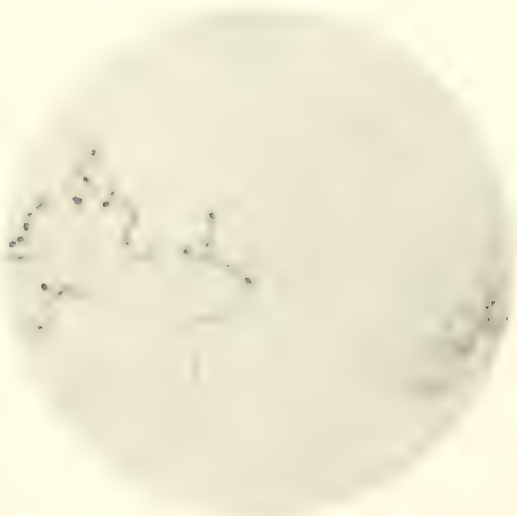
Case II. showed colon bacilli in smear preparation, in the culture, and in the fibrin. Case XVIII. showed in the smear preparation and in the fibrin B. mucosus capsulatus, colon bacilli, and B. aerogenes capsulatus. Culture in this case showed colon bacilli and B. mucosus capsulatus.

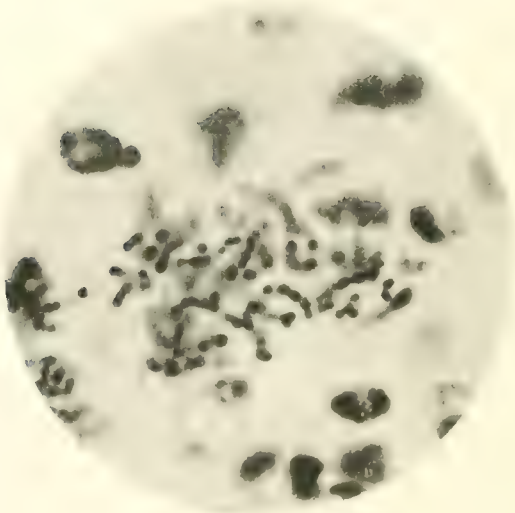
In Case III. the colon bacilli and B. aerogenes capsulatus were present in smear preparation and in the fibrin. Culture showed the colon bacilli only.

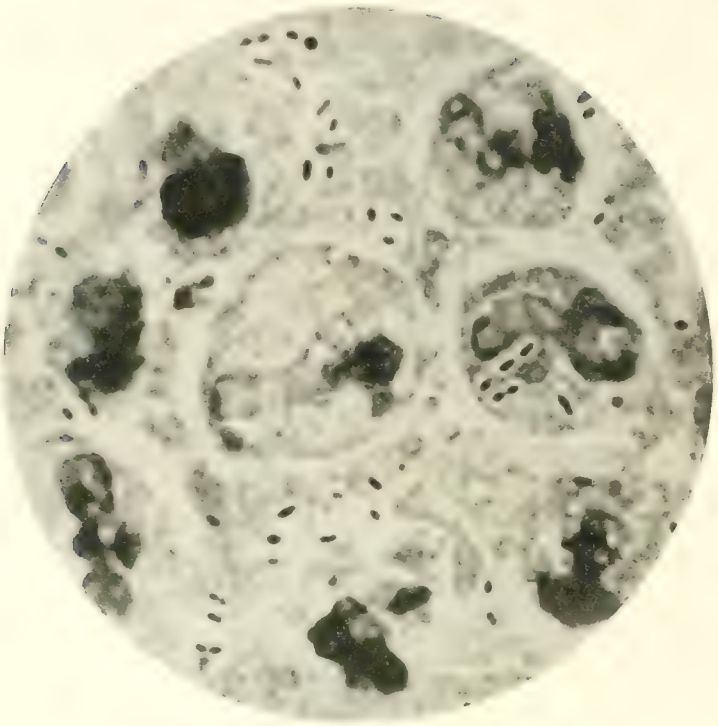












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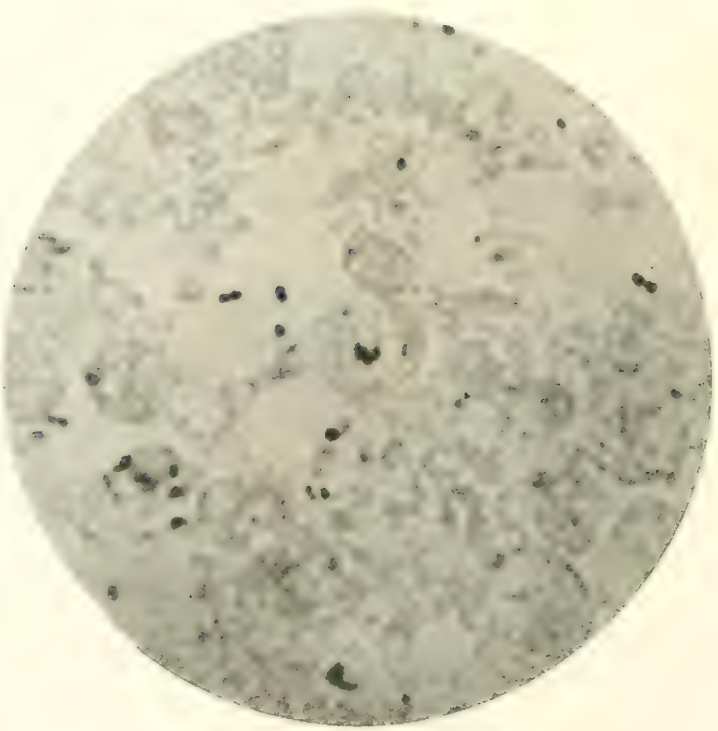

Case XIV. showed the colon bacilli and B. mucosus capsulatus in the smear preparation and culture, while the colon bacillus alone was present in the fibrin.

It is to be concluded from the observations in these nineteen cases that in most cases of acute peritonitis with fibrinous exudation bacteria are present in large numbers in the fibrin.

(I am greatly indebted to Dr. J. H. Wright for his encouragement and advice in carrying out this work. I also wish to thank the staff of the Massachusetts General Hospital for their kindness in allowing me to use their material.)

DESCRIPTION OF PLATES.

Plate XXIII.

Fig. 1. Case IV. Smear preparation of abdominal pus, showing bacillus aerogenes capsulatus and bacillus mucosus capsulatus. Stained by Gram's method, eosin and methylene blue.

Fig. 2. Case IV. Section of fibrinous exudate, showing leucocytes and the bacillus aerogenes capsulatus in the meshwork of fibrin. Stained by Gram's method, eosin and methylene blue.

Fig. 3. Case XI. Section of fibrinous exudate, showing masses of streptococci, fibrin, and leucocytes. Stained by Gram's method and thionin.

Fig. 4. Case XV. Smear preparation of pus in the abdominal cavity, showing streptococci and degenerated leucocytes stained by Gram's method, eosin and methylene blue.

Fig. 5. Case XV. Section of fibrinous exudate, showing streptococci, fibrin, and leucocytes. Stained by Gram's method and Aurantia.

Plate XXIV.

Fig. 1. Case IX. Smear preparation of pus in the abdominal cavity, showing pneumococci free and within the leucocytes. Stained by Gram's method, eosin and methylene blue.

Fig. 2. Case IX. Section of the fibrinous exudate, showing pneumococci, fibrin, and degenerated leucocytes. Section stained by Gram's method and Aurantia.

(The photographs were made by Mr. L. S. Brown in the Clinico-Pathological Laboratory of the Massachusetts General Hospital.)

TRANSPLANTATION OF ARTERIES.

JOSHUA C. HUBBARD, M.D.

(*For the Division of Surgery of the Medical School of Harvard University.*)

Until recently the surgery of arteries has been confined to the repair of tears in the vessel wall. In those cases where the tear is of small extent the defect is closed by sutures. When the tear extends more than one-half across the vessel it has been shown by Murphy (N.Y. Med. Record, Jan. 16, 1897) that simple suturing is unsatisfactory, because by so extensive a wound of the wall many of the vasa vasorum are destroyed. As a result, the nutrition of the wall is so reduced that it eventually sloughs along the suture line. To repair an artery, when so severely torn, resort must be had to either Murphy's invagination method (N.Y. Med. Record, Jan. 16, 1897) or to the magnesium cylinders of Payr (Arch. f. Klin. Chir., 1900, H1).

Fine silk has been found to be the best suture material (Doerfler, Beitr. z. klin. Chir., 1900) of such a size that it will fill as nearly as possible the needle holes in the vessel wall. The needles are to be the finest which can be handled. Doerfler (Beitr. z. klin. Chir., 1900) proved experimentally that sutures which appear in the lumen of the vessel do not act as foreign bodies and cause thrombi. He advocated, therefore, passing the sutures through all the layers, because more practical than including only the adventitia and media. Jacobsthal, who examined some of Doerfler's specimens microscopically, found that in a few days a thickening of the endothelium occurs, which surrounds the stitches and thus shuts them off from the lumen of the vessel.

The problem before me in this experimental work has been the radical cure by surgical means of aneurisms of the abdominal aorta. As many abdominal aneurisms have a branch to some part of the alimentary tract coming from the sac, the first step in the cure of the aneurism proper must concern itself with the treatment of this branch. One of the larger

branches to the intestine cannot be tied off, for by so doing the circulation to that portion of the intestine is suddenly changed. We have learned from cases of thrombosis of the mesenteric arteries that the branches going to the intestine are practically end arteries, and that the sudden stopping of the circulation in one of them results in gangrene of that portion of the intestine supplied by it. The problem then is to deal with this branch coming from the sac, in such a manner that it will permanently continue to supply blood to its portion of the intestine, or will be shut off so slowly that time will be given for the establishment of a collateral circulation. Transplantation of this branch to some neighboring part of the aorta will fulfill these requirements, if the anastomosis will remain patent permanently or for a sufficient length of time. My work was thus reduced to establishing first the practicability of transplanting arteries. All my experiments were done on dogs. The carotids were chosen as the vessels to be transplanted because of their accessibility and size.

From the work already done by Murphy it was evident that it was useless to sew the end of a divided vessel into a hole in another because of the sloughing along the suture line from the destruction of the vasa vasorum. In order to minimize this destruction as much as possible, I began by doing a lateral anastomosis, the technic of which was as follows: The dog was given a subcutaneous injection of morphine, and then etherized. The skin of the neck was cleaned by shaving and washing with corrosive. Each carotid was isolated, and one divided between ligatures at the base of the neck. The divided vessel was pulled across the neck, and the point decided upon where the anastomosis was to be made. To control the circulation during the operation a strip of gauze was passed around the divided vessel some distance from the end and two others around the intact carotid, one above and one below the point chosen for the joint. These bands were pulled tight enough to control the circulation and held by hemostats. A narrow strip was excised from the wall of each vessel, and the corresponding edges of the slits thus made were sewed together by No. 4 silk on fine curved

needles, the sutures including all the layers. After finishing the suturing, the joint was tested by releasing the distal gauzes first. Any oozing was controlled by another stitch or two or by light pressure for a moment. By then loosening the proximal controlling gauze strip, the full blood pressure was allowed to come on the anastomosis.

EXPERIMENT I. — At end of operation doubtful whether pulsations felt in the transplanted artery. Dog died on fifth day. The carotid found shut off proximal to the anastomosis by a stitch too deeply placed. The anastomosis patent, as shown by the passing of air from a blow pipe, through the anastomosis, from the transplanted vessel and out the distal end of the carotid.

EXPERIMENT II. — At end of operation blood passed through anastomosis. Dog etherized nineteen days later. Vessels dissected out and pulsations almost as strong in the transplanted vessel as in the main artery. On section vessel walls very much thickened at the site of the anastomosis and the lumen lessened. Portion of a silk stitch free in the lumen; slight evidence in the wall of another suture, otherwise none seen from the inside. The connection between the vessels was through several small holes.

EXPERIMENT III. — At end of operation blood passed freely through anastomosis. When animal killed, about one month later, vessels thrombosed.

EXPERIMENT IV. — At end of operation doubtful whether blood passed through anastomosis. When killed later, vessels thrombosed.

EXPERIMENT V. — After ligating the carotid, it was not divided, but drawn across the neck and anastomosed to the other. At end of operation the blood passed through the anastomosis. When killed two days later thrombus at site of anastomosis.

Thinking that perhaps the anastomosis which was found patent at the end of nineteen days might have been done unconsciously in such a way that intima was brought in contact with intima, I then changed my technic. A slit was made in each vessel, and sutures were so placed that intima was brought in contact with intima.

EXPERIMENT I. — At the end of the operation blood passed through the anastomosis. When animal killed three days later, clot found at the site of the anastomosis.

EXPERIMENT II. — At the end of operation blood passed through the

anastomosis. When animal killed two days later, thrombus found at the anastomosis and at the site of one of the controlling gauzes.

EXPERIMENT III. — No. 1 silk and fine cambric needles used. At end of operation blood passed through the anastomosis. When animal killed four days later, air could be blown through the main vessel, but not through the anastomosis, which was obstructed by a clot.

I then changed the technic entirely, and made an anastomosis in the following manner. Both carotids were isolated. One was tied low in the neck. A controlling gauze band was placed about it, high up in the neck. One vessel was divided just above the tie. The end of the vessel was split, so that two flaps were made. Controlling gauzes were placed around the main carotid. A wedge-shaped piece was cut from its wall. The lumen of the divided vessel was placed over the hole, and the two flaps were carried around the undivided carotid and sutured to each other and the sheath of the vessel. This part of the operation was done several times before it was satisfactory. The first two times the small size of the hole prevented a free flow of blood into the transplanted vessel. At the third attempt the hole was enlarged, and the blood passed through feebly. A stitch was required at the angle of the flaps to prevent oozing. Two days later the animal was etherized, and the vessels cut down upon. The condition was then the same as at the end of the operation, the pulsations being strong in the main vessel beyond the anastomosis and feeble in the transplanted one. Fifteen days after the first operation the animal was killed. Air from a blow-pipe passed through the anastomosis and out of the end of the transplanted vessel, but before it came through the main vessel a small, soft, dark clot was forced out.

I have not been able to further test this method from lack of material, but it seems superior to the others in that it minimizes the handling of the vessels, and the bruising of the intima causes, for thrombus formation, and that it can be done with few sutures, perhaps all being outside the lumina. Care must be taken that the hole is large, and that the flaps do not act as ligatures. A criticism which might justly be

made of the earlier methods is, that later the line of the suture might weaken and the vessel wall give way. By this method there is no fear of this, as the wall is stronger after the operation than before.

In all the above experiments it was possible to make an anastomosis which would not leak, no matter what method was used. In seven of these nine experiments an anastomosis was made which transmitted the circulation satisfactorily for the time being. In one the anastomosis was patent five days after the operation, though the main vessel was thrombosed, and in another, where the result was perfect two days after operation, at fifteen days after operation a small and apparently recent clot was found in the main vessel, though the anastomosis itself was functionary, and in a third there was perfect success nineteen days after operation, when the dog was killed. When it is realized that the vessels with which I have been working are about the size of the radial artery in man, and even smaller when the circulation is controlled, it will be appreciated that the mechanical difficulties of placing the sutures without injuring the intima are great. If results can be obtained under these circumstances which are at all satisfactory, how much more hopeful is the outlook when the vessels are of large size.

All of the above experiments were carried out on the carotids. The technic of transplanting a branch of the aorta would not differ. The cord would be deprived temporarily of its blood supply, and the result of this might be questioned. In two animals I attempted to transplant branches of the aorta, and controlled the circulation long enough to perform the operation. Neither of the cases was successful as far as the anastomosis was concerned, the first because the transplanted branch was too small to work on, and the second because it was under so much tension in its new position that during the muscular spasms of death from a subcutaneous injection of strychnia it was torn away from the aorta. In neither case, however, did the animal show any ill effects from the temporary anemia of the cord.

Doctor Matas (Ann. of Surgery, Feb., 1903) has already

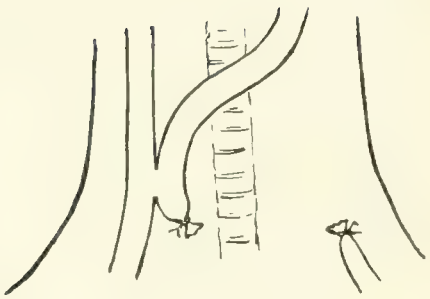

FIG. 1.

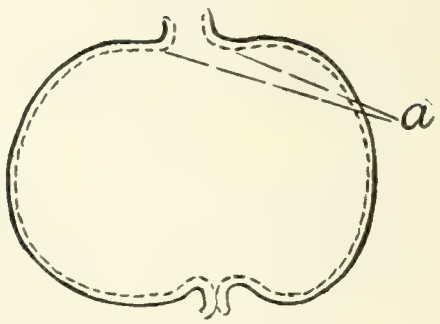

FIG. 2.

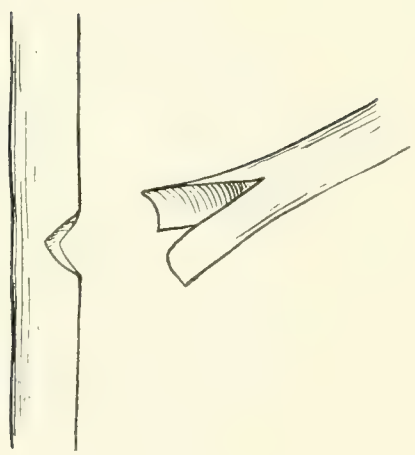

FIG. 3.

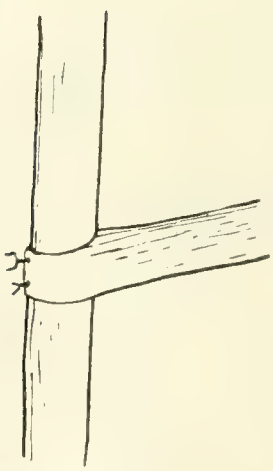

FIG. 4.

published a report of three cases of aneurism cured by suturing the sac, leaving a lumen when possible. This portion of my original problem has, therefore, been already solved. By combining his technic with mine, it seems that it should be possible to cure an aneurism of the abdominal aorta. The aneurism can be sutured by the method of Matas, preserving its lumen, and any branches which arise from its sac and are too important to obliterate can be transferred to another portion of the aorta.[1]

[1] I should hesitate to present such a paper as this, which leaves so many points unsettled, were it not that this is the first report by the Committee on Surgical Research, to whom I am indebted for my opportunity to experiment. As I hope some time in the future to continue this work, I make my offering now simply as a preliminary report.

DESCRIPTION OF PLATE XXV.

Fig. 1. Scheme for carotid transplantation.

Fig. 2. Cross-section of vessels at anastomosis, showing the vessel walls turned, bringing intima against intima. A. intima.

Figs. 3–4. Last method of anastomosis described.

THE EFFECT OF X-RAYS ON LIVING TISSUE.[1]

SEABURY W. ALLEN, M.D.

(*For the Division of Surgery of the Medical School of Harvard University.*)

From the conflicting statements about the effects of X-rays in therapeutic work, experiments have been made on various sorts of living tissues, in the hope that if definite pathological results could not be found in human tissues, one might reason by analogy from experiments along other lines. In attempting to eliminate errors from the results there arose so many problems in electricity, physics, biology, and pathology as to make it almost impossible to come to accurate conclusions, so that this report is made rather as a preliminary than as a final one.

With the exception of the cases treated, and unless otherwise stated, the method of exposure to X-rays was to have the object on an insulated support as nearly as possible in the line of the angle of reflection of the cathode stream, so that the greatest amount of X-rays were received. Between the tube and object was a grounded aluminum screen, the wire to the ground and the two feed wires to the tube being as far from the object as possible, so that the magnetic field about the tube was reduced to a minimum. Electroscopic tests on the distal side of the grounded screen were negative.

The apparatus used was usually a twelve-inch Heinze coil, which is a high potential, but not a high frequency, machine, and the quality of light was such as to show clearly the bones of the wrist. Changes of air, temperature, light, and moisture were guarded against as far as might be.

The material worked with included vinegar worms (angelula aceti), protozoa, capillaries of frogs, etc., frogs' hearts, tortoise hearts, beans, lupin seeds, human leucocytes, clinical cases of cancer and tuberculosis, and "burned" human skin.

[1] Only through the kindness of Mr. Walter J. Dodd, of the Massachusetts General Hospital, have I been able to do a large part of this work. I have also to thank him for clinical material and for much valuable advice and assistance.

VINEGAR WORMS.

1. Several drops of vinegar containing numerous worms were exposed for thirty-six minutes at forty-five centimeters' distance from the anode, and observed under a low-power microscope during the whole time. One-half hour after exposure the majority of the worms were dead, the others being coiled up and making irregular movements. Two controls unchanged.

2. Similar experiment repeated at the same distance for eighteen minutes. Result in half an hour, many worms dead or dying, but not so many as before. Control unchanged.

3. Experiment repeated with a Kinraide high-frequency coil. Result in half an hour only a few worms dead. Control unchanged.

4. Same experiment without grounded screen; twenty-one minutes' exposure. Result same as in No. 1. Controls unchanged.

5. Two similar amounts of vinegar taken. (*a*) Exposed to X-rays without grounded screen nineteen minutes, ten centimeters from anode. (*b*) Similarly exposed, but protected from X-rays by sheet lead, being in the magnetic field. Result: (*a*) worms nearly all killed. (*b*) Between one-third and one-half killed. Examined immediately after exposure.

6. At forty centimeters' distance for one and one-half minutes; no result.

7. At forty centimeters from the anode, "low" penetrating light, bones of the hand being faintly seen. Exposure thirty minutes, no change seen.

From these experiments it appears that long exposures were necessary to affect the worms; that less effect was obtained from the high frequency apparatus; that X-rays together with an active magnetic field were more fatal than the magnetic field alone, and that a highly penetrating light was more harmful than a low one.

PROTOZOA.

A two-weeks' old infusion of hay showed under the microscope many rapidly swimming protozoa, each surrounded with a membrane and containing moving protoplasm and a nucleus. Groups of protozoa were frequently seen feeding on clumps of dirt or chains of bacteria.

1. Exposed forty-five minutes at ten centimeters from anode and observed under microscope during whole time. After the first five minutes the protozoa were no longer seen to feed in clusters, but became separated with possibly a livelier motion. At end of exposure a few were motionless.

One and a half hours later nearly all were dead; a few were swimming slowly. Control unchanged until the water dried up.

2. Similar experiment, similar result in thirty minutes.

3, 4, and 5. With exposures of varying duration under thirty minutes no appreciable effect, except the failure to feed in groups after the first few minutes.

6. Exposure to high frequency brush discharge for thirty seconds killed all individuals. Control unchanged.

CAPILLARY CIRCULATION.

1. The hind feet of a chloroformed frog were pinned out so that the capillary circulation in the web could be seen under the microscope, one microscope being used for each foot. Foot (*a*) exposed to X-rays sixteen minutes at fifteen centimeters' distance. Foot (*b*) protected from X-rays by sheet lead. Both feet otherwise under the same conditions. At end of exposure the capillaries in web (*a*) showed dilatation to nearly double the size of web (*b*). (There seemed to be a slight dilatation in web (*b*), probably from the irritation of the pins and stretched condition of the web.) No emigration of leucocytes could be seen. Fifteen minutes later the capillaries had almost regained their former size; the light was again turned on and the capillaries again dilated.

2. The same frog twenty-four hours later; same experiment repeated, using the previously protected foot for

exposure. Same effect noticed in fifteen minutes. Control unchanged.

3, 4, and 5. Attempts were made to perform similar experiments on three tadpoles, two white mice, and one guinea-pig, in each case chloroform being used; but owing to the impossibility of keeping the animals quiet, the field under the microscope could not be observed throughout, though it was thought that the same result appeared. In the guinea-pigs' mesentery a marked dilatation was seen in three minutes. But as the capillaries in the peritoneum dilate anyway when the abdomen is opened, one can conclude nothing from this.

FROGS' HEARTS.

1. A frog's heart was excised and kept moist with normal salt solution, beating eighteen to the minute, and exposed to X-rays for eleven minutes at twenty-five centimeters' distance. At end of nine minutes the heart's rate was still eighteen. At end of ten and a half minutes only a faint contraction could be seen; in eleven minutes no contraction; no recovery in one hour.

2. Two frogs used. Frog (*a*) killed by electrocution; frog (*b*) by chloroform. Hearts of both excised and kept moist with salt solution, heart (*a*) beating strongly at thirty-two to the minute, heart (*b*) beating weakly at twenty-eight. After an exposure to X-rays of one minute and ten seconds at twenty-five centimeters' distance from the anode, heart (*a*) had ceased beating. After exposure at same distance for one minute, heart (*b*) had ceased beating. No recovery of either heart in half an hour.

KYMOGRAPHIC TRACINGS OF HEART ACTION IN LIVING ANIMALS.

Seven frogs and one tortoise were used. After pithing the brain and spinal cord so that the animal would keep still, the thorax and pericardium were opened and the heart made to write kymographic tracings in the ordinary way. Twelve records in all were made. Owing to the kymograph being

small and the X-rays not immediate in their action it was not easy to show the effect in one revolution of the drum, unless it ran so slowly that the excursions of the writing point overlapped. The entire animal was protected from the X-rays by sheet lead, except for a window which just allowed the auricles and ventricles to receive the light, so that whatever effect was obtained must have been solely on the heart. Varying lengths of exposures were made between five and thirty minutes; in no case was there any effect with less than three minutes' exposure, and usually there was none under ten minutes. In all seventeen tracings were made, four of which showed no change. Of the other thirteen all showed a shorter excursion of the writing point, and five of the thirteen showed both a shorter and a slower excursion, after the X-rays were turned on. The failures were in fresh, strongly beating hearts, and the inhibitory effect was best seen when the hearts were either tired or overloaded. (See Plate XXVI., 1.) The tracing reproduced here was made by a tortoise's heart. In this case the writing point was an electric spark arranged to make a record without friction. The smaller frogs, especially the females, were found unsatisfactory. Professors William T. Porter and W. B. Cannon have been kind enough to point out one or two possible errors in these experiments, such, for instance, as the lack of a control frog and the failure to be sure that the temperature of the air did not vary during the experiments, but it would seem as if these results, taken in connection with those of the excised hearts, were at least suggestive of a direct inhibitory effect.

BEANS.

Twenty-eight beans (Faba vulgaris) were planted in two flower-pots. The first pot received in all one hour and forty minutes of X-rays, as near to the pot as the growth would allow. The second pot received no X-rays. The beans in the X-rayed pot appeared above the earth first and averaged a greater height than those in the other pot. Thirteen beans grew up in the X-rayed pot and seven only in the control.

To obviate any error in the previous experiments, especially with regard to the electric field, seven beans were planted in each half of the same pot, and the control side protected with one-quarter inch sheet lead during the exposure. X-rays were given for ten minutes daily for seven days, a total of one hour and ten minutes. In three weeks the conditions were as shown in the picture. (See Plate XXVI.)

Similar results were obtained with two other pots of beans, one pot of nasturtiums, one of lupins, and one of mustard, though the difference between those exposed to X-rays and the controls was not so marked as in the more rapidly growing beans. In all cases the plants that received the X-rays did not survive so long as those not receiving the rays, though the former appeared above the earth first and grew to a greater height. They appeared to be over-stimulated. In all cases the plant received the same amount of water (measured) and daylight.

To see what effect the X-rays would have on a full-grown plant, some weeds were picked in a swamp early in spring. After an exposure of ten minutes daily for ten days within ten centimeters of the anode, no variation from the control could be seen. A similar failure was found with willow-buds.

HUMAN LEUCOCYTES.

In seven individuals white and red blood counts were made, three slides of leucocytes being counted in each case. Then X-ray exposures were given for ten minutes in the ordinary way and the blood again counted immediately. In three of the cases the first count was made from one ear, then the exposure made on the other ear, and the second count immediately taken from the exposed ear. In one the exposure was on the forearm, and in three on the face; in these cases the second count was taken from a point at least two inches distant from the place where the first had been taken, in order to avoid any leucocytosis from the irritation of the first prick.

Results: No variation was found in the red cells.
Leucocytes:

CASE 1. — Face.	Before exposure . . .	5,000
	After " . . .	9,600
CASE 2. — Arm.	Immediately after dinner.	
	Before exposure . . .	11,200
	After " . . .	13,600
CASE 3. — Ear.	Before " . . .	7,000
	After " . . .	6,600
CASE 4. — Face.	Before " . . .	6,000
	After " . . .	8,200
CASE 5. — Cheek.	Before " . . .	6,500
	After " . . .	9,200
CASE 6. — Ear.	Before " . . .	6,800
	After " . . .	8,140
CASE 7. — Ear.	Before " . . .	6,800
	After " . . .	11,500

Cases 2 and 3 were healthy individuals exposed for experiment only. All the other cases were exposed for existing malignant or tubercular disease. In one case (3) there was no increase in the number of white corpuscles, and in the other six an average increase of nearly three thousand. If these results can be substantiated later, they will at least suggest that the presence of an increased number of leucocytes in tissues exposed to the X-rays has a bearing upon their curative action in superficial lesions. Whether or not the cure is due to the phagocytic action of the leucocytes can be only a matter of conjecture.

PATHOLOGICAL SECTIONS.[1]

In all, eighteen cases have been studied clinically and histologically: nine of epithelioma of the face, all of which

[1] My thanks are due to Dr. E. H. Nichols, Dr. Walter C. Howe, and Dr. Channing C. Simmons for valuable assistance in studying the microscopic slides. Also to Dr. Simmons for the use of one of his cases.

healed from a clinical point of visio; one of carcinoma of the cheek, not healed; three of carcinoma mammæ, none healed; one of scrofuloderma, healed; one of lupus vulgaris, healed; two X-ray burns of three years' standing, healed after excision of the burned skin; and one case of frog skin exposed fifty-seven minutes.

NINE CASES OF EPITHELIOMA OF THE FACE, ALL OF AT LEAST TWO YEARS' STANDING, HISTOLOGICAL DIAGNOSES HAVING BEEN MADE BEFORE BEGINNING TREATMENT.

The sections studied were all taken after sufficient exposure to X-rays to have produced a slight dermatitis and a partial healing, and were excised either from a healed area or from the margin of the ulcer that was in process of healing. All of the lesions from which the sections were excised healed up later and have remained healed for a year. In other words, the cancers were disappearing at the time the sections were excised.

This case will serve as a type of this group. (See Plate XXVII., 1 and 2.) Diagnosis of epidermoid cancer was made histologically. Duration of disease seven years. After ninety minutes of exposure during two months, my notes say, "Scab almost gone. Given final exposure of seven minutes at three and a half inches from anode. Specimen taken from healed area in front of nose, including nodule." (See Plate XXVII., 3.)

This specimen shows "a typical rodent ulcer entirely covered by epithelial cells which dip down in places. Necrosis and hyaline degeneration occasionally." [1]

Here, then, a bridging of the epidermis has taken place over a typically malignant nodule, which had been unhealed up to the time the X-rays were given. The areas of degeneration and necrosis after exposure and skinning over of the epidermis are no more than might be found in any such

[1] Report of Dr. Howe.

growth, whether treated by X-rays or not; in other words, there is no appreciable effect on the cells microscopically, although healing apparently took place over them.

In contrast to the superficial lesions above described, the following sections from deeper lesions were examined: From a large rapidly-growing, squamous-cell carcinoma of the face and neck a specimen was taken from the subcutaneous tissue early in the treatment. This specimen shows "many epithelial pearls, some containing leucocytes; new connective tissue, hemorrhage in small areas, deeper masses of epithelial cells showing necrosis and softening. In places the epithelial cells are perfectly preserved. Cells of the sebaceous glands normal. A certain amount of endarteritis. Two mitoses seen." [1]

After thirty X-ray exposures by Mr. Dodd, causing considerable dermatitis and a slight macroscopic improvement, a piece was excised from the same area as before. "Included masses of epithelium are more numerous. Epithelial pearls show degeneration and contain leucocytes. Many lymphoid and plasma cells. Hemorrhage on surface of section. Mitoses rare." [2] (Plate XXVIII., 1 and 2.)

"None of these specimens show any satisfactory evidence from a microscopic standpoint that the carcinoma cells are in extensive process of resorption." [3]

In other words, there are no changes in the microscopic elements to be shown after thirty treatments by X-rays, although clinically the case was slightly improved.

This case became rapidly worse and disappeared. He is doubtless dead.

Tumor of breast. "Narrow columns of epithelial cells with a relatively large amount of connective tissue stroma. Scirrhus cancer." [3] After sixty-seven X-ray exposures a section was removed from the same area as before. "The skin was slightly thickened and everywhere deeply reddened with superficial, cicatricial contraction. Microscopic examination

[1] Report of Dr. E. H. Nichols.
[2] Report of Dr. Howe.
[3] Report of Dr. J. H. Wright.

shows it to be made up of a plexus of quite small epithelial cells separated by relatively dense bands of connective tissue. The cells in general were small and slightly irregular, but there were numerous mitoses present."[1] (Plate XXVIII., 3 and 4.)

In other words, there were no microscopic changes, except on the skin, referable to the X-ray treatment, although the case clinically improved; in fact, the carcinoma had become more medullary, if anything. The patient is still living, two and a half years after beginning treatment.

An X-ray burn of three-years' standing, resulting from a single radiographic exposure in a neighboring town, was excised under ether. Microscopic examination: "Considerable increase of connective tissue of the corium and of subcutaneous tissue. In places there is infiltration of the corium and subcutaneous tissue with small cells. Some of the lymph channels of the corium are markedly dilated. Epidermis of one part of the section is lacking, and there is necrosis of the underlying tissue. The Malpighian layer of the epidermis shows marked irregularity in the outline of the inferior border and sends downward into the corium short processes."[2] (Plate XXVIII., 5.)

Here are evidences of destruction of the superficial tissues similar to what might be produced by any caustic, but in the deeper layers there was no microscopic change in the cellular elements nor were any macroscopic changes seen during the operation of excision. In other words, the destructive effect was seen only superficially.

The skin of a frog exposed fifty-seven minutes at fifteen centimeters' distance from anode and immediately hardened in Zenker's fluid, showed on section no variation from the control, except one dilated blood vessel containing leucocytes.

In several of the above specimens there are evidences of necrosis, endarteritis, increased formation of connective and elastic tissue, and dilated blood vessels and lymph channels. But these changes do not occur sufficiently often to draw conclusions from them. I cannot substantiate the statements

[1] Report of Dr. William F. Whitney.
[2] Report of Dr. J. H. Wright.

made by certain writers[1] with regard to necrosis of deep tissues or alterations in deep malignant growths referable to X-ray treatment.

Apparently, then, X-rays exert their action on the surface only; just as one's clothing or an aluminum screen will generally prevent a burn of the skin, so does the skin prevent a burn of the underlying structures. If it were possible to expose deep malignant growths without the intervention of any structure, very likely they would be cured as the surface ones are. While a burn is not necessary to produce healing in an epithelioma, a slight dermatitis hastens it. Of course, if necrosis is produced by an excessive exposure of the diseased tissues there will be both destruction of the tissue and the disease, but in my nine cases of epithelioma there was no more degeneration or starvation of the cellular elements than there might be in any cancer, yet the cases all healed; besides, the resulting scars were too pliable, and the tissue underneath too much filled out to have followed much necrosis. Evidently there is some action of the X-rays that is not a necrotic one, but which heals certain skin diseases and improves certain deep ones, but just what the cause of the healing is cannot be determined. Electrification may have something to do with it, as this factor cannot be entirely ruled out. On the other hand, it is well known that when an electrified body is passed through the path of X-rays it loses its charge, and it may be that the normal electrical action which always accompanies life is in some way similarly altered. But in the light of the above experiments a simpler hypothesis is that the irritant effect produced by the exposure brings more blood to the part and also gives a greater opportunity for phagocytosis. By the dilatation of the superficial capillaries the disappearance of pain may be explained on the grounds of diminished deep congestion caused by increased superficial congestion. This action, while being similar to that of any counter-irritant like iodine or a hot-water bag, is, however, usually more than temporary.

[1] Sterne, Indiana Med. Journal, August, 1902. Grubbé, N. Y. Med. Rec., Nov. 1, 1902. Hopkins, Phila. Med. Journal, April 15, 1902, etc.

When we consider that a low penetrating light (poor in X-rays) is more effective than a high penetrating light (rich in X-rays), we must infer that the clinical effects are not due to X-rays so much as they are to some other unknown phenomenon. That this phenomenon is not simply the brush discharge is suggested by the fact that the most effective tube is the low one, from which the brush discharge is weak. Furthermore the same results are apparent, when the electrostatic effect is ruled out by a grounded screen. Discouraging as are the ued results on deep malignant growths, there is no doubt that with rare exceptions the cases treated are relieved of pain, gain in weight, improve in general condition, and live longer than they would have otherwise.

CONCLUSIONS.

1. The effect of prolonged X-ray exposures on vinegar worms and protozoa is fatal.

2. On superficial capillary circulation the effect is like that of an irritant, producing vaso-dilatation. The relief of pain in cases of deep malignant growths may be explained by this phenomenon.

3. On the heart in cold-blooded animals X-rays act as an inhibitor.

4. On growing plants the effect is distinctly stimulating, in fact, over-stimulating. On full-grown plants it is not apparently harmful.

5. Exposures produce immediately a local increase in the number of leucocytes in the blood. This is consistent with the irritant effect upon the skin and capillaries.

6. On surface malignant growths the effect is curative in a great majority of cases, the cure not necessarily being the result of necrosis.

7. On deep malignant growths there is no microscopic change to be found in the pathological or normal cell elements.

8. Excessive exposure on healthy skin produces sloughing of the superficial tissues, leaving a low-grade, sluggish

ulceration which heals slowly or not at all. Permanent dilatation of the capillaries and a scarcity of granulation tissue and blood vessels are common in such ulcerations.

9. Clinical effects are not due to X-rays so much as they are to some other unknown, but closely allied phenomenon.

EXPLANATION OF PLATES.

PLATE XXVI.

1. Tracing of tortoise heart. Record written on kymograph with electric spark, to avoid friction. X-rays turned on at first white line above tracing, turned off at second white line.

2. Seven beans planted in each half of pot. Right-hand half exposed seventy minutes to X-rays. Left-hand half protected during exposure by one-quarter inch sheet lead.

PLATE XXVII.

1. Epidermoid cancer of nose. Before treatment.

2. Same case as 1, after total exposure to X-rays of one hour and thirty minutes, during a period of two months.

3. Section of skin from "healed" area from case shown in 1 and 2.

4. Same specimen as 3, with high power.

PLATE XXVIII.

1. Squamous cell carcinoma of cheek. Section of tumor showing infiltration of subcutaneous tissue at beginning of treatment.

2. Same case as 1. Section from similar portion of tumor, showing no change in appearance after thirty X-ray exposures.

3. Scirrhus carcinoma of breast. Section of tumor showing columns of atypical epithelial cells.

4. Same case as 3, after sixty-seven X-ray exposures.

5. Section of margin of ulcer produced by X-ray burn of skin of three years' standing, showing changes only in superficial tissues.

FIG. 1.

FIG. 2.

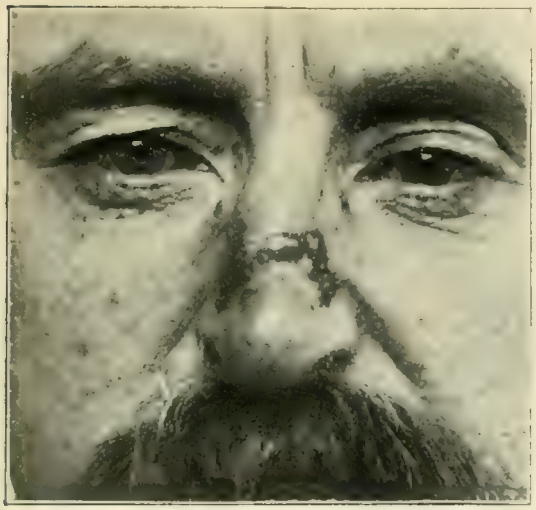

FIG. 1.

FIG. 2.

FIG. 3.

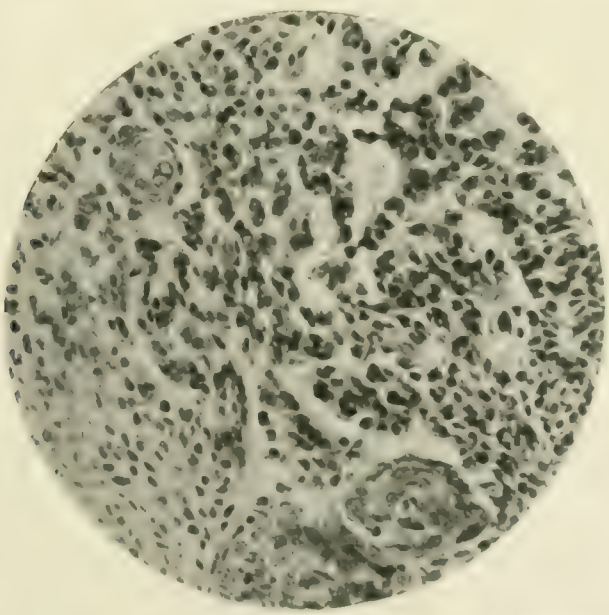

FIG. 1.

FIG. 2.

FIG. 3.

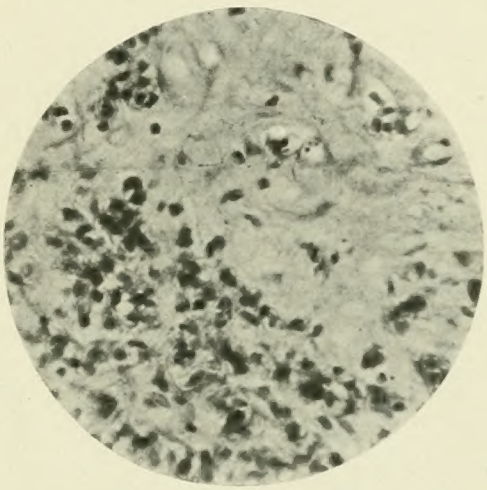

FIG. 4.

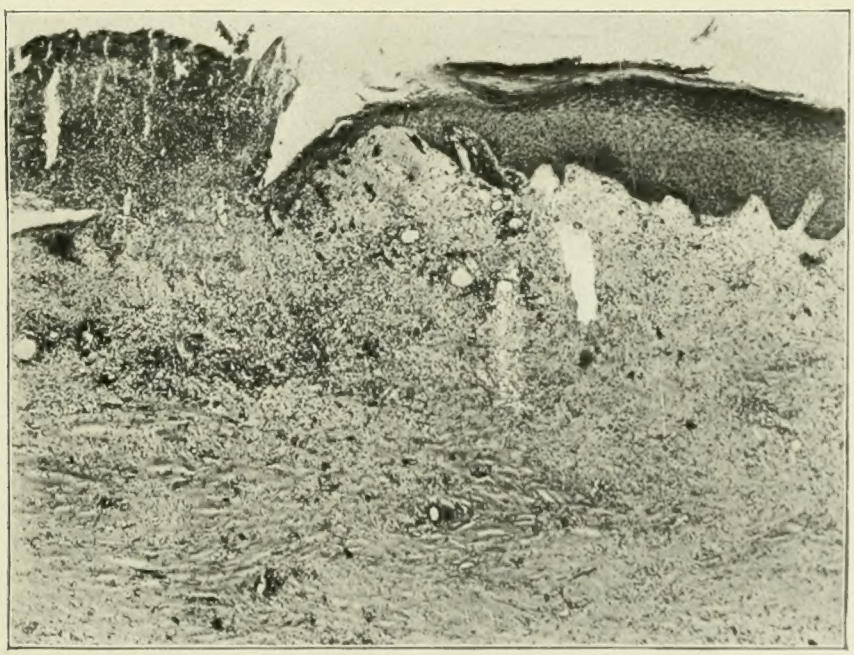

FIG. 5.